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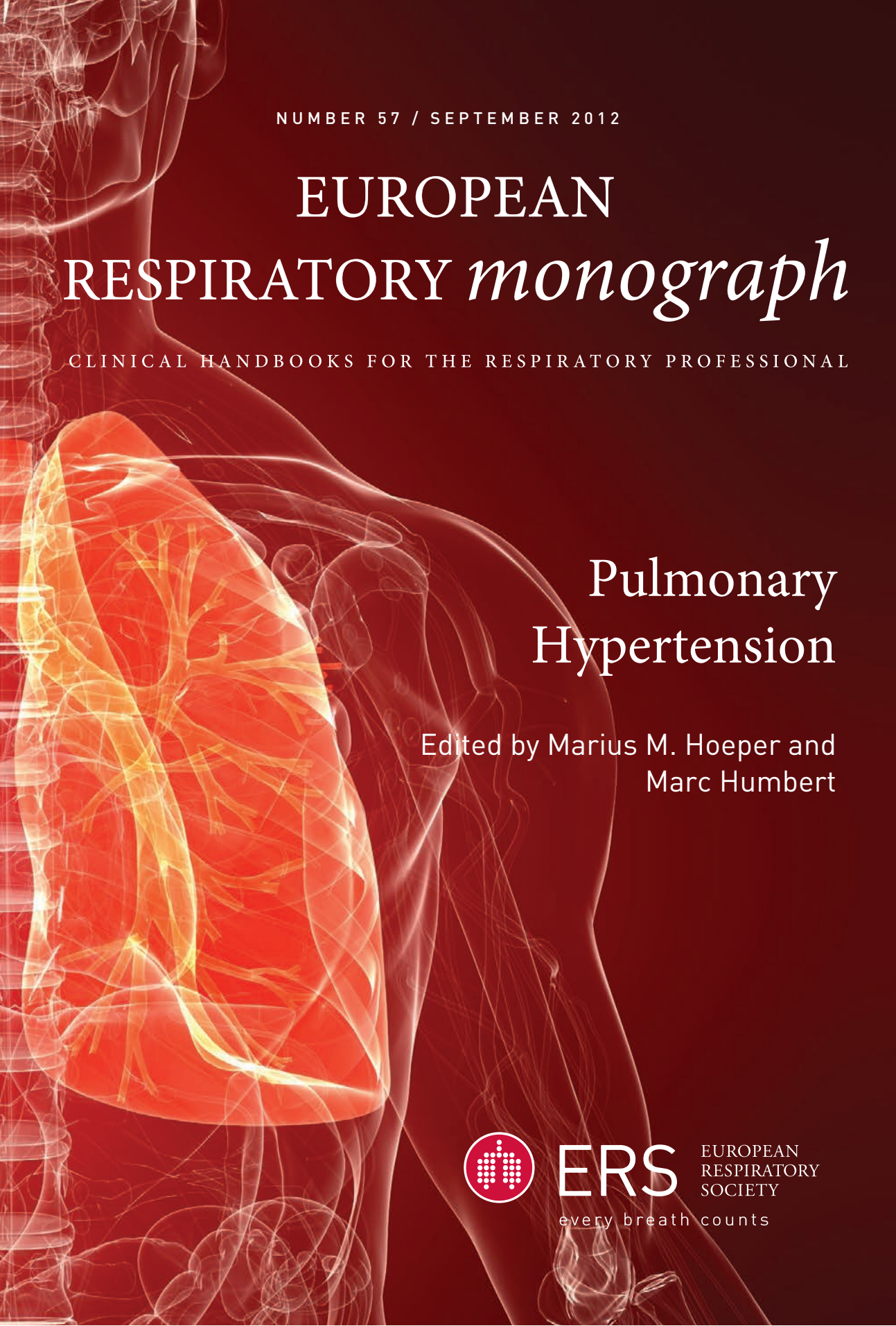

# Pulmonary Hypertension

Edited by Marius M. Hoeper and Marc Humbert

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European Respiratory Monograph 57, September 2012

# Pulmonary Hypertension

Edited by Marius M. Hoeper and Marc Humbert

Editor in Chief
Tobias Welte

This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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# Guest Editors

Marius M. Hoeper

Marius M. Hoeper was educated at Hannover Medical School (Hannover, Germany), where he specialised in respiratory medicine and intensive care medicine. In 1992, he received a 2-year grant from Germany's National Research Foundation for a post doctorial training position at the University of Colorado (Denver, CO, USA). Following this he returned to the Hannover Medical School, where he now holds the position of Senior Physician in the Department of Respiratory Medicine. He is in charge of the pulmonary hypertension programme and is the clinical director of the medical intensive care unit. His main scientific interest lies in the field of pulmonary hypertension, where he has published more than 160 papers. In addition, Marius serves as a regular reviewer for major medical journals in his field and is a member of the *American Journal of Respiratory and Critical Care Medicine* editorial board as well as an associate editor for the *European Respiratory Journal (ERJ)*. Marius was a task force member at the 3rd World Symposium on Pulmonary Hypertension held in 2003 (Venice, Italy) and was a task force chair at the 4th World Symposium on Pulmonary Hypertension held in 2008 (Dana Point, CA, USA). In addition, he has been an author and section editor for the 2009 European Guidelines for Pulmonary Hypertension.

Marc Humbert

Marc Humbert is Professor of Medicine at the South Paris University (Le Kremlin-Bicêtre, France). In addition to his academic responsibilities, he is consultant and specialist at the National Referral Centre for Pulmonary Hypertension, Department of Respiratory and Intensive Care Medicine, Hôpital Bicêtre, Assistance-Publique Hôpitaux de Paris, (Paris, France). Marc is Director of the INSERM UMR-S 999 "Pulmonary Hypertension: Pathophysiology and Innovative Therapies" and Director of the ''Thorax Innovation'' University Hospital Department. Marc is Vice Dean of the South Paris University School of Medicine, President of the Research Committee and Vice President of the Board of Directors of the Assistance-Publique Hôpitaux de Paris. He was the Editor of the proceedings for 4th World Symposium on Pulmonary Hypertension held in 2008. He is currently Chief Editor for the *European Respiratory Review* (*ERR*) and is an Associate Editor for the *European Respiratory Journal* (*ERJ*). He has published widely in the fields of pulmonary hypertension and pulmonary inflammation, and was awarded the European Respiratory Society Cournand Lecture in 2006 with a lecture on "The Burden of Pulmonary Hypertension". Marc has also received the Descartes-Huygens Prize from the Royal Netherlands Academy of Arts and Sciences.

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# Preface

Ten years ago, the prognosis of patients with pulmonary hypertension (PH) was poor. At that time, no pharmaceutical treatment was effective in all patients. This has changed dramatically with the introduction of inhaled prostacyclin as maintenance therapy. Endothelial antagonists and phosphodiesterase inhibitors, both based on pathophysiological considerations and used as monotherapy or in combination, have extended the spectrum of treatment possibilities. All of the drugs used have been shown to be efficient with regard to the different outcome measures, including haemodynamic parameters, exercise tolerance and life quality. As a result, observational studies have demonstrated an incredible increase in the life expectancy of patients with PH.

When the development of new therapies began, idiopathic pulmonary arterial hypertension (IPAH) was the focus of research. The therapeutic success in this field initiated studies in patients with different forms of secondary PH, starting with PH associated with connective tissue disease, followed by patients with interstitial lung fibrosis or chronic thromboembolism, and then moving on to those with chronic obstructive pulmonary disease (COPD) or congestive heart failure. Huge randomised controlled trials have been performed for most of these indications, meaning it has been possible to establish very specific algorithms for diagnosis and treatment with regard to the baseline disease causing PH. Due to the intensive collaboration of PH researchers all over the world and a special effort within the PH community, guidelines have been developed and quickly corrected in the light of new experiences and findings, making PH an example of standardised management of disease on a worldwide scale.

However, the story of PH continues. Basic research in PH has raised interesting new concepts for further treatment options. The pharmaceutical industry and public research institutes are also working together to consider different methods of diagnosis and treatment. And personalised medicine based on pathophysiological concepts and risk stratification is no longer just a vision, as work is underway to improve outcome of patients with PH.

This issue of the *European Respiratory Monograph* summarises the current pathophysiology, diagnosis, and pharmacological and non-pharmacological treatment of PH. The best experts in the field have contributed to this book, which should be of interest not only to basic scientists and clinicians, but also to those in the pharmaceutical industry, as it provides in-depth consideration of the future of PH. The issue is also the first to include continuing medical education (CME) questions (accredited by the European Board for Accreditation in Pneumology (EBAP)), meaning it will be particularly attractive to those in training. To earn 5 CME credits, simply read the issue and answer the questions at the back of the book and provided online.

I want to personally congratulate the Guest Editors of this excellent *Monograph*, which provides an excellent overview of PH. Marius and Marc, thank you very much for a fantastic collaboration. I am convinced that this *Monograph* will be a major success.

Editor in Chief
Tobias Welte

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# Introduction

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Pulmonary arterial hypertension (PAH) is characterised by vasoconstriction, thrombosis and remodelling of the small pulmonary arteries, leading to chronic pre-capillary pulmonary hypertension (PH) and fatal right heart failure. PAH is a rare and devastating condition with a prevalence of less than 50 cases per million adults in the European Union and a median survival of less than 5 years after diagnosis. As emphasised in the updated PH classification, there are many other causes of PH and its global burden is currently unknown and certainly underestimated. Indeed, common diseases such as chronic obstructive pulmonary disease (COPD), pulmonary embolism and hepatosplenic schistosomiasis are frequent causes of PH worldwide. In addition, post-capillary PH due to chronic cardiac diseases is very common in general and specialised practice. Altogether, PH and its consequences on the right heart contribute markedly to the global burden of chronic cardiopulmonary diseases.

Initial symptoms of PH are nonspecific and often unspectacular, and may delay diagnosis and appropriate management. Lack of awareness often explains why symptoms are attributed to a more common cardiorespiratory disease. As a result, there is a substantial delay of more than 1 year in the diagnosis and initiation of appropriate therapy. It is important to highlight that management requires a thorough diagnostic work-up, including right heart catheterisation (RHC), which is the gold standard to confirm diagnosis, define whether PH is pre- or post-capillary and evaluate its severity. It is widely accepted that early intervention (and prevention, whenever possible) of PH is of utmost importance to improve quality of life and long-term outcomes.

The current issue of the *European Respiratory Monograph* provides updated information on the various forms of PH from respected leaders in the field of pulmonary vascular medicine. Our ambition is to help healthcare professionals and medical students to better understand and manage PH in the modern era. The more we learn about these diseases, the more we understand how complex the management of these patients can be. Advanced therapies are often beneficial in patients with PAH but can worsen other forms of PH. Delaying appropriate treatment can have detrimental, sometimes life threatening, consequences that should remind us that the management of patients with severe PH should always involve expert centres.

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# Chapter 1

# Pulmonary vascular disease: an historical perspective

*Tim Higenbottam*

**SUMMARY: The history of pulmonary vascular disease has followed a remarkable course. It epitomises all that is good in medicine's development. Early history involved description of the clinical presentation and natural history of the disease. These approaches were enhanced by the introduction of measurements such as chest radiography, ECGs and right heart catheterisation(RHC). A major advance occurred with detailed work on the structural abnormalities from histopathology. Finally, attempts to classify the different forms of pulmonary vascular disease were made.**

**The structural and physiological observations and advances in vascular pharmacology allowed the "modern" treatments to be introduced: prostacyclin ($PGI_2$), bosentan, sildenafil and inhaled nitric oxide (NO). Each had a place and analogues.**

**We are now entering a new phase, which has benefited from lung transplant surgery giving access to patients' lung cells for studies of mechanisms. Advances in genetics and the ability to identify the mutations that result in heritable pulmonary arterial hypertension (PAH) have pinpointed the target mechanisms for new therapies. This is not "controlling the pathophysiological abnormalities" but introducing therapies that may reverse the structural abnormalities of the disease. PAH is leading a modern revolution in medicine's development.**

**KEYWORDS: Bone morphogenetic protein receptor II, dexfenfluramine, lung transplant surgery, prostacyclin, pulmonary hypertension, vasodilator therapy**

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## History of and firm foundations for future therapies

Many of us were drawn to medicine by the hope of introducing new treatments for patients. In the last 30 years, this has proven possible for pulmonary arterial hypertension (PAH) and other forms of pulmonary vascular disease. For every step in the advance of care and medical treatments we

owe an enormous debt of gratitude to the many careful physicians, pathologists and scientists who have uncovered the true nature of these diseases.

A wonderful review of many of these early achievements in pulmonary hypertension (PH) has been written by Al Fishman, one of the pioneering physiologists in the field of pulmonary vascular disease [1]. He elegantly outlines the contributions of many of his contemporaries, whose work has led to the current and indeed future PAH therapies.

## The diagnostic pattern of symptoms and physical signs

Current knowledge of pulmonary vascular disease has developed over a period of 150 years. The first step was the development of a set of diagnostic criteria, enabling the physician or surgeon to recognise the disease and differentiate it from other causes sharing its symptoms and physical signs. Once they had been precisely described, the natural history of each disease could be followed. There were practical advantages of accurate diagnostic criteria and a defined natural history: doctors were able to give an accurate prognosis to the patient. Furthermore, from the phenotype of the disease, certain disease mechanisms could be discerned.

## Specific diagnostic tests

An important step for pulmonary vascular disease was the introduction of cardiac catheterisation by André F. Cournand and Dickinson Richards, and Werner Forssmann [2]. This technology provided a means of diagnosing and assessing the severity of hypertension. Diagnostic tests gave precision to the definition of the phenotype of the illness. For the development of new therapies, cardiac catheterisation offers an outcome measure upon which the efficacy of new medicine can be determined.

## The vital role of histopathology

It is a sad reflection that, like many fatal illnesses, pulmonary vascular disease became better understood as a result of the histopathological examination of *post mortem* material, and by linking the structural abnormalities of organ and tissues with the natural history of the disease. As we will describe later, a number of scientists have made significant contributions to our knowledge of pulmonary vascular disease.

## Molecular mechanisms of the disease phenotype

By combining the precision of diagnostic tests with detailed description of the structural changes of organs in the disease state, it becomes possible to correlate structure and function. Such work has often provided an effective method of identifying new therapies. As we will see later, this is exactly what happened with PAH.

The 1950s to 1980s was an era of detailed physiological description of the major body systems. The many receptors that regulate these functions were described in detailed pharmacological studies, and molecules were identified that either antagonised or stimulated the receptor to correct pathophysiological abnormality. This was also a period of expansion in the pharmaceutical industry, and one in which it seemed possible to treat many important diseases. Sadly, in the last two decades, progress in the development of new treatments has slowed. This is believed to be a result of failure to further advance the understanding of disease.

Recently, it has become possible to sub-classify phenotypes of monogenetic diseases according to genotype associations. This has introduced a radical new method of medicine development: the underlying molecular mechanisms of certain diseases have been identified by their genetic abnormality. Innovative PAH treatment will almost certainly be developed through this approach.

In PAH, it has become possible to describe one molecular mechanism in detail, and link this to a phenotype of the disease. There is a haploid insufficiency of bone morphogenetic receptor type II

(BMPR II) that leads to the enhanced risk of developing idiopathic PAH (IPAH). Duchene muscular dystrophy is another disease in which genetic abnormality has led to small molecule therapies directly affecting the molecular mechanism of the disease. Here, patients with a nonsense mutation were treated with an oral therapy called Ataluren® (PTC Therapeutics, South Plainfield, NJ, USA), which overcomes such mutations. In a phase II study (communication from PTC Therapeutics), the low dose of the drug reduced the deterioration of the 6-minute walking distance (6MWD). Further studies are needed, but this encourages the view that new ways of treating molecular dysfunctions are available. Similarly encouraging results have been reported in cystic fibrosis (CF) from a recently completed phase III study (communicated by the company PTC Therapeutics). There are 1,500 mutations of the CF transmembrane conductance regulator (CFTR) ion channel; in one, the G551D mutation which is found in 4% of patients, a new oral therapy called Kalydeco® (Vertex Pharmaceutical, Cambridge, MA, USA) has been approved by the Food and Drug Administration (FDA). This agent overcomes the failure of the CFTR protein to open properly. There are a number of other approaches to the mutations in CFTR, which have been co-funded by the Cystic Fibrosis Foundation in Bethesda (MD, USA) [3]. The inherited molecular mechanism leads to a distinct phenotype. It has proved possible to target this aberrant molecular mechanism to restore normal function and lessen the intensity of the disease. This approach is likely to speed up the discovery of new medicines in pulmonary vascular diseases.

In this chapter we will follow the history of many of the forms of pulmonary vascular disease, especially those for which new therapies have emerged. These advances have provided treatments but we are just at the beginning of a new age of molecular-targeted medicines for pulmonary vascular disease.

# Early understanding of PH

## Clinical description of PH

Early descriptions of PH were made during the last quarter of the 19th century. It was proposed that increased resistance in the pulmonary circulation in chronic lung disease gave rise to right ventricular (RV) enlargement and the signs of failure. Case reports and series of patients were described who became disabled because of breathlessness on exercise. They were often cyanosed with the development of peripheral oedema, and had signs of cardiac enlargement and elevated central venous pressure (CVP). The Graham Steell early diastolic murmur, heard over the right parasternal edge, was attributed to elevated pressure in the RV causing pulmonary valve regurgitation [4]. This was one of the first detailed descriptions of the physical signs associated with the symptoms characteristic of PH. It was followed by a paper by Ernst von Romberg, who also described the clinical features of PH a few years later in 1891 [5].

As is often the case in medicine, the mechanism for the murmur was later refuted. It took almost 100 years to have access to all the measurements necessary to attribute the murmur to another mechanism [6]. This is a common occurrence in medical science; new observations become established until refuted by new technology. However, the value of Graham Steell's work was the description of the cluster of symptoms and signs of PH, which continue to be appreciated.

## Histopathology of pulmonary vascular disease

The modern concept of PH was introduced by Moschowitz, who recognised PH in various forms of heart disease, in chronic lung disease and in pulmonary arterial disease [7]. He not only described the signs and symptoms associated with PH but also initiated the idea of the importance of thrombotic obstruction of the small pre-capillary arterioles, which has become increasingly import in recent times.

Pulmonary arteriosclerosis is another name that was given to the pathological changes of pulmonary arteries in patients with PH. Posselt found that 40% of patients with mitral valve disease had these abnormalities in their pulmonary arteries [8].

### Modern measurements of pulmonary vascular disease and histopathology

Greater precision in diagnosis began with the introduction of chest radiographs and ECGs. These investigations enabled confirmation of enlargement of the heart and changes of RV. As many PH patients died soon after diagnosis, it was possible to use histopathological studies to link evidence of intimal thickening of the small arteries, together with an increase in their muscularity, to prior symptoms of PH [9, 10]. In the 1940s, unexplained PH was first reported. De Navasquez described three patients with PH in whom cardiac or lung disease could be demonstrated at *post mortem*. They had the features of small vessel disease in the pulmonary arteries [11]. Names for this disease have varied and have included primary PH, which was used until 1998.

## The description of phenotypes of pulmonary vascular disease

### Cardiac catheterisation

Three physicians were awarded the Nobel Prize for medicine in 1956 for their work on introducing the means of measuring normal and abnormal physiology of the heart and of the pulmonary and systemic circulation [2]. Their work led to a better understanding of the circulation, which included visualisation of the greater blood vessels. Working in the Bellevue Service of Columbia University College of Physicians and Surgeons (New York, NY, USA) in the 1930s, André Cournand and Dickinson Richards pioneered right heart catheterisation (RHC). Their work was performed on animals and was shown to be a safe technology in humans through the self-experimentation of Werner Forssmann. Combined cardiac catheter research made it possible to provide a definite diagnosis of PH. It also led to the accurate diagnosis of pulmonary embolism and thrombotic disease of the pulmonary circulation.

#### *Paul Wood*

Whilst working in the Royal Postgraduate Hospital in London (UK), Paul Wood greatly expanded knowledge about PH in all its forms through the use of cardiac catheterisation. He was able to categorise the different causes of PH and measure their severity. Paul Wood described PH according to the elevation of pulmonary artery pressure ($P_{pa}$), where normal mean pressure is below 13 mmHg [12]. He proposed that the factors that increased $P_{pa}$ included: reduction of the total cross-sectional area of the pulmonary vascular bed; increased pulmonary blood flow; reduction in alveolar oxygen tension; elevation of left atrial pressure; certain drugs. By describing these mechanisms, he provided structural and physiological analysis that contributed to the description of the different phenotypes. He was the first to propose that the occlusion of two-thirds of the pulmonary circulation was required to raise the $P_{pa}$; in his time, noradrenaline and phenylephrine were also recognised to cause a sharp rise in $P_{pa}$, when injected *i.v.*

Paul Wood provided an integrated view of the symptoms, signs and catheter results that led to a definition of PPH, linked to the pathophysiology and unexplained by known cardiac and respiratory causes. He developed a classification of the many causes of PH (table 1).

#### *David Dresdale*

David Dresdale, who had worked with Cournand and Richards, separated PH into the primary (unexplained) and secondary forms of heart and lung disease [13]. He also considered the importance of therapy [14], and introduced *i.v.* tolazoline for the acute reduction of $P_{pa}$.

#### *Donald Heath*

Donald Heath advanced the structural and physiological knowledge of PH by adding a further level of refinement to the histology of PH. He did this by combining cardiac catheter studies and detailed

**Table 1.** Paul Wood's classification of the many causes of pulmonary hypertension (PH)

| |
|---|
| Embolic and thromboembolic PH |
| Primary or idiopathic PH |
| Specific forms of pulmonary arteritis (schistosomiasis, polyarteritis nodosa, Löffler's syndrome, disseminated lupus) |
| Pulmonary plethora (septal defects and patent ductus arteriosus with elevated blood flow) |
| Mitral stenosis |
| Chronic cor pulmonale |

*post mortem* examination. The catheter studies were able to separate most forms of secondary PH from IPAH or PPH. He provided detailed descriptions of the characteristic small pulmonary artery changes of PPH (which he also called "idiopathic pulmonary hypertension") [15]. These small vessel changes were confined to arteries of less than 100 μm in diameter, where a distinct muscular media appeared between the two elastic laminae and where there was severe intimal fibrosis. One area of controversy remains, concerning the plexiform structures reported by a number of pathologists as a characteristic of idiopathic PH or PPH. Indeed, some referred to IPAH as "plexiform pulmonary hypertension". In 1960, Naeye described these structures in both primary and secondary forms of PH [16]. It took some 28 years to remove the term "plexiform pulmonary hypertension", and it was not until the World Health Organization (WHO) Evian meeting on PPH in 1998 that the terminology was removed.

### *Wagenvort and Wagenvort*

Wagenvort and Wagenvort greatly expanded the descriptive work of the histopathology of pulmonary vascular disease [17].

### *William Evans*

William Evans made the link between small artery pathology and widespread obstruction of the pulmonary circulation in PH. He demonstrated the impact of occlusion and narrowing of the small arteries [18] using an injection of bismuth oxychloride in gelatine in the *post mortem* lungs to provide a detailed angiogram. He was able to separate thromboembolic disease from IPAH, as the occlusions were seen centrally and were associated with segmental loss of perfusion. In PPH, occlusion of the muscular and smaller arteries was associated with a widespread and diffuse pruning of the vascular bed.

It was a further decade before Jack Reeves quantified and correlated the numerical loss of vessels in PPH to the histopathological changes [19, 20]. At the time of death, up to 70% of the small arteries are obstructed. These arteries were shown to be affected by intimal thickening and smooth muscle hypertrophy.

### The physiological cause of PH

In summary, the widespread obstructive lesions were found to be associated with concentric or eccentric narrowing of the internal lumen of the small arteries. The narrowing and ultimate loss of these blood vessels massively increased the resistance to blood flow through the lungs. This in turn evoked a response from the RV, raising the pressure in order to maintain systemic blood flow. Disability in the form of exercise limitation and syncope is the result of RV failure [21].

## Early considerations of pharmacological treatment

Treatment for many of the so-called secondary forms of PH was directed at the underlying cause, *e.g.* correction of the mitral stenosis by surgical treatment or use of oxygen in chronic obstructive pulmonary disease (COPD).

### Vasodilators

For PPH, Dresdale proposed vasodilator therapy in the form of *i.v.* tolazoline. This reduced the pressure elevation and increased the cardiac output during infusion [14]. Wood had proposed the use of the ganglion blocker hexamethonium to achieve vasodilation. His work led to the trial of *i.v.* acetylcholine to reduce vascular resistance in the lungs [22].

### Anticoagulants

Early ideas on the mechanisms of intimal thickening and the possible links with platelet dysfunction and intravascular thrombi led to the proposal for the use of anticoagulant therapy in idiopathic PH [23].

## Modern therapies for PH

### The National Institutes of Health PPH Registry

The 1980s were a period of rapid expansion of knowledge about PH. The National Institutes of Health (NIH) established a registry of patients with unexplained PH [24]. The resulting prospective study was able to report on the survival of a cohort of PPH patients over a period of 5 years. Factors that were identified as predictors of poor prognosis included the estimate of total pulmonary vascular resistance and the measurement of low cardiac output. The preponderance of females with PPH was confirmed.

### The first successful heart–lung transplants

The first successful heart–lung transplants were undertaken in 1982 in patients with PH [25]. This became the first successful therapy to extend the survival of patients. The results of the NIH register were helpful in guiding the selection of patients who should be offered lung and heart–lung transplant surgery.

A major research advantage resulted from the success of lung transplant surgery. Patients often donate their lungs for research, meaning cells and tissues could be studied. This was the basis for the discovery of many of the cellular mechanisms of PH and helped establish their link with the mutations associated with heritable PAH.

### Long-term vasodilator therapy

Calcium channel blocker (CCB) therapies, approved for the treatment of systemic hypertension, were used in patients who were in the early stages of IPAH and who had shown evidence of a vasodilator response [26]. This treatment was not free of the serious side-effects of the significant falls in systemic blood pressure, which could result in syncope.

### Anti-coagulant therapy

During this time, Valentine Fuster reported an observational study that strongly indicated the use of anticoagulants in the management of PPH patients and their increased survival [26].

### Reeves and Rubin

In 1982, Lewis Rubin, whilst working for Jack Reeves, undertook an acute study of *i.v.* prostacyclin ($PGI_2$) in primary PH [27]. This showed very good pulmonary vasodilation which was dose dependent. Also it was possible to show an increase in cardiac output without a large fall in systemic blood pressure. $PGI_2$ had been discovered by Richard Gryglewski in 1980 when he was working with John Vane [28]. It was a naturally occurring vasoactive regulator that that was a powerful vasodilator and inhibitor of platelet aggregation.

### Long-term intravenous $PGI_2$

During this time, at Papworth Hospital (Cambridge, UK), a number of patients with PPH were dying whilst awaiting a suitable donor on the lung transplant waiting list. To enable survival until transplant surgery, we set up treatment with $PGI_2$. This involved an electronic syringe pump and infusion through a subcutaneously tunnelled line. The first patient improved strikingly and gained exercise tolerance sufficient to return to work [29]. We found that the 6-minute walk test (6MWT) was a good means of following up patients with PPH and this was used to evaluate the efficacy of the $PGI_2$ treatment [30].

### Iloprost

Further studies indicated that $PGI_2$ and its analogues can be used long-term to treat PPH [31, 32]. This was a powerful positive proof of concept that persuaded the Wellcome Trust to undertake a pivotal study of long-term $PGI_2$. The study was a randomised controlled trial, which enabled submission for approval to market $PGI_2$ as a treatment for PPH. The results were impressive as $PGI_2$ extended survival significantly and improved exercise tolerance, measured using the 6MWT [33]. It was the first medical therapy to gain marketing approval from the regulatory agencies for the treatment of PPH.

Within the space of 12 years, a new and effective treatment was introduced, leading to prolongation of life and improved quality of life [34]. A place for anticoagulants was found and a massive search began for therapies that were simpler than long-term infusions of $PGI_2$.

### IPAH patient selection for lung transplant surgery

The selection of patients for lung transplant surgery began to be based on the clinical failure to respond to these early IPAH treatments [35]. Patients were offered lung transplant surgery if the treatments failed to control their deterioration.

## Knowledge gained from fenfluramine and dexfenfluramine side-effects

Advances in the understanding of a disease are not always the result of treatments that bring benefits. In 1967–1972 an epidemic of PPH was described in Switzerland, Austria and Germany, which was associated with the widespread use of a treatment for obesity called aminorex [36]. There appeared to be a temporal relationship between the widespread use of this prescribed medicine and the onset of the PPH, but as there was no control group, a definitive cause could not be identified.

In single case reports, a number of agents, such as phenformin (an oral anti-diabetic) and fenfluramine (another anti-obesity therapy), were linked to the development of PPH. However, as their use and the disease itself were rare, it was not possible to attribute causation.

In the PH clinic of the AP-HP Hôpital Antoine Béclère (Paris, France), Francois Brenot described a cohort of PPH patients who had all been prescribed the anti-obesity drugs (anorexigen) fenfluramine or dexfenfluramine [37]. As with aminorex, there was a strong suspicion that the drug was the cause, but causality could not be proven from the observational study.

### The International Primary Pulmonary Hypertension Study

As a result of the uncertainty about the safety of anti-obesity therapies, such as fenfluramine, a retrospective epidemiological study was performed to determine whether there was a causal link with PPH.

The International Primary Pulmonary Hypertension Study (IPPHS) used a case–control design, recruiting 3–4 controls from general practices that had cared for known (and validated) patients with PPH. Both cases and controls underwent a detailed enquiry into their past use of therapies, performed by non-medical but carefully trained interviewers who did not know the purpose of the study. Drug usage was checked against general practitioner prescribing records in a subset of patients. All patients were reviewed by an independent expert panel, which applied the accepted criteria for the diagnosis of PPH. Other factors were also assessed regarding the risk of developing PPH, including obesity, cirrhosis of the liver and HIV infection [38].

This landmark study first separated PPH from secondary PH patients, then used a controlled design to calculate the risk factor odds ratio (OR). It clearly showed that there was a highly significant association between the use of anorexigens and the risk of developing PPH. Those who had taken drugs for over 12 months were especially at risk. There was a reduction in risk if patients had stopped taking the drug for more than a year before. This fulfilled the Bradford Hills test for causality, namely dose dependency and a temporal relationship associated with a highly significant OR when compared with controls. Biological plausibility was missing, and to this day, the precise mechanism for PPH in fenfluramine patients remains unknown, although serotonin was raised as a potential mechanism. Other factors were also confirmed as conferring a risk; HIV infection and cirrhosis both had significant ORs for the development of PPH compared with controls, but no increased risk was found for obesity.

### *Important outcomes of the IPPHS*

The study was particularly important as it involved the collaboration of a number of PH clinics in Europe and the USA. This collaboration led to successful trials of newer therapies. It also led to the re-classification of PH in 1998.

A further important outcome was the recognition of another potential mechanism of the disease. Both fenfluramine and dexfenfluramine caused a reduction in plasma levels of serotonin through increased release from intracellular stores by inhibition of the serotonin transporter [39]. This is the putative neural mechanism in reducing obesity by lessening appetite. Through potentiation of the vasoconstrictor effects of endothelin (ET)-1, local release of serotonin could enhance pulmonary artery narrowing [40].

## Imbalance of vasoactive agents derived from the endothelial cells

Success with $PGI_2$ was limited by the difficulty of the long-term *i.v.* infusion system. There was a movement to simplify the delivery of $PGI_2$ analogues and develop new oral therapies.

### Alteration of the normal rate of production

Once it had been shown that *i.v.* $PGI_2$ could lengthen survival and improve the quality of life of IPAH patients, concentrated research began to identify other disturbances of vascular control.

It was not selective, acting on all blood vessels including veins. As it acted on both pulmonary and systemic arteries, the "trick" of *i.v.* infusion was that it was possible to carefully titrate the dose until systemic blood pressure began to fall. At this point, optimal pulmonary vasodilation will have occurred and no further dose increase will be needed. This simple approach prevented the often dangerous fall in systemic blood pressure that occurs when other longer-acting vasodilators are used to treat IPAH. The search began for other vasoactive therapies that could achieve the same result.

### Brian Christman

In an elegant study in 1992, Brian Christman was able to show that PH patients had a lower rate of production of $PGI_2$ than normal patients [41]. $PGI_2$ synthase enzyme expression in the pulmonary

vascular endothelium was later shown to be reduced in PPH patients [42]. $PGI_2$ deficiency was therefore proposed as a mechanism for PPH.

### M. Yanagisawa

In 1988, M. Yanagisawa and colleagues identified a powerful vasoconstrictor called ET, which derived from the endothelial cells [43]; from this, ET-1 was identified as a physiological regulator of vascular tone. It was shown that PPH patients had elevated levels of ET-1 [44] and evidence of increased expression was found in their lungs.

### Robert Furchgott

Robert Furchgott proposed that endothelial-dependent relaxation was a result of nitric oxide (NO) [45]. As with $PGI_2$, it was some time before it could be shown that the total body production rate of NO was reduced in IPAH patients [46]. This confirmed earlier work, which showed that the pulmonary arteries of patients with PH had a reduced NO release [47]. Finally, reduced expression of NO synthase, the enzyme responsible for NO production, was demonstrated in the pulmonary arteries of PPH patients [48].

### Imbalance of vasoactive endothelial factors

These observations led to the idea that an imbalance of vasoactive endothelial factors may contribute to the development of PH. In IPAH and in other forms of PH, there was overproduction of the vasoconstrictors, such as ET-1 and serotonin, but underproduction of the vasodilators, such as $PGI_2$ and NO [49]. It was thought that this imbalance contributed to the phenotype of IPAH. Therapies could then be rationally developed to restore the balance.

## ET-1 receptor antagonists and further new therapies

### Tracleer® (bosentan)

Tracleer® (bosentan; Actelion, San Francisco, CA, USA) was the product of Dr Martine Clozel whilst she was working at Roche (Basel, Switzerland). It was the first ET-1 receptor antagonist to be brought into clinical use.

Initial use of bosentan was delayed as it was difficult to decide on the dose. Dr Clozel developed a wonderful study design in which normal volunteers received an infusion of ET-1 and the antagonists were administered in increasing doses until the effects of the infusion were completely blocked. This provided the dose needed for treatment.

As co-founders of the pharmaceutical company Actelion, Martine Clozel and her husband were successful in getting Tracleer® (bosentan) approved for the treatment of IPAH in 2001. As an oral agent with high efficacy, it soon became the first-line therapy for IPAH [50]. It was also found to be successful in PAH secondary to systemic sclerosis [51].

There followed two similar products. Ambrisentan (Volibris®; GSK, Brentford, UK), which is free of liver complications and interactions with warfarin, was approved in 2007 in the USA and 2008 in Europe. Thelin (sitaxentan; Pfizer, New York, NY, USA) was initially approved in Europe but was voluntarily withdrawn by Pfizer in 2010 because of liver toxicity.

### $PGI_2$ analogues

These include beroprost, which is an oral analogue of $PGI_2$, and treprostinil, which can be administered intravenously, *s.c.* and by inhalation. Iloprost (Ventavis®; Actelion Pharmaceticals Ltd,

Allschwil, Switzerland) has both an *i.v.* and inhaled formulation [52]. These have all been approved and again offer the patients a wider choice of therapy.

### Inhaled NO

With the identification of NO as an endothelium-derived relaxing factor (EDRF), NO was used during catheter studies in IPAH patients [53] and was shown to be a selective pulmonary vasodilator. It was quickly used for the treatment of PPH in neonates, where it gained approval for use in acute management after birth [54, 55]. Delivery of the gas in patients on assisted ventilation can be relatively easily achieved.

### Inhaled NO in COPD

In order for ambulatory patients to inhale NO, it was necessary to develop a pulsing device that delivered a small volume of the gas with each breath. This proved successful in COPD patients with PH [56]. The device used conserved gas, reduced the risks of overdose and protected the healthcare professional caring for the patient. It also resulted in improved distribution of ventilation, as shown by a fall in arterial carbon dioxide tension ($P_{a,CO_2}$) and a significant fall in pulmonary vascular resistance, together with a trend in increased exercise endurance. Interestingly, it is the only vasodilatory therapy in COPD patients with PH that does not cause a fall in arterial oxygen tension ($P_{a,O_2}$).

### Sildenafil

Viagra® (sildenafil; Pfizer), a treatment of erectile dysfunction, became of interest as it works by inhibiting the enzyme guanylate cyclase, which breaks down cyclic guanosine monophosphate (cGMP), produced through NO stimulation of the enzyme. As such, it amplifies the actions of NO. The enzyme guanylate cyclase is highly expressed in the arteries of the penis, enabling penile erection. The enzyme is also highly expressed in the pulmonary circulation of male humans and many animals. Here, NO seems to regulate the recruitment of the pulmonary circulation during exercise [57].

In a proof-of-concept study, we compared long-term inhaled NO with sildenafil and found that in IPAH patients, only sildenafil improved the 6MWD, long-term inhaled NO did not. The explanation for this was simply that patients did not use the inhaled NO (unpublished data).

This simple proof-of-concept study provided sufficient support for the performance of a pivotal study of sildenafil, and subsequently led to the approval of sildenafil use in IPAH patients [58]. As it was very simple to use and relatively free of side-effects it became the first line of treatment.

## Pulmonary thromboendarterectomy

Since 1970, pioneering physician Ken Moser has worked with several cardiothoracic surgeons and has slowly acquired the experience to identify and then undertake surgical removal of chronic thromboembolic obstruction of the major pulmonary arteries. This work was led by the University of California (San Diego, CA, USA) and the San Diego Veterans Medical Center (San Diego). The first series of patients to be described had advanced PH, class IV disease (according to the New York Heart Association (NYHA) criteria) [59]. Pulmonary vascular resistance fell after surgery from $897 \pm 352$ to $278 \pm 135$ dyns·s·cm$^{-5}$. 35 patients survived (mean follow-up 28 months). This caused a highly specialised evaluation of all PH patients to exclude this condition and to define those most likely to benefit from surgery.

## Guidelines for the treatment of PH

Guidelines for PH treatment became necessary as more treatments were discovered. The first guidelines were developed by the European Society of Cardiology (ESC) [60] and later extended to

the USA. These provided a logical series of algorithms for the treatment of patients with PH, including IPAH, based on the level of evidence. They have been updated by the ESC and the European Respiratory Society (ERS) to include the use of combinations of agents with different targets [61].

## Re-classification of PH

In 1973, WHO called a conference on PH [62]. It set out a rational basis for the classification of the many different forms of PH. It was built on the work of Paul Wood and David Dresdale.

In 1998, the Evian WHO conference on PH was called to consider a re-classification of PH. The re-classification was published electronically and gave rise to the adoption of the term ''pulmonary arterial hypertension'' to refer to patients in whom the disease was presumed to involve the small pulmonary arteries. By this time, it was recognised that $PGI_2$ treatment did not help patients with PH who were suffering from pulmonary veno-occlusive disease (PVOD). In 2003, during the 3rd World Symposium on Pulmonary Hypertension in Venice (Italy), the clinical classification of PH, initially adopted in 1998 during the 2nd World Symposium, was slightly modified (table 2). ''Familial pulmonary arterial hypertension'' was used to describe patients with a family history of the disease [63].

**Table 2.** Revised clinical classification of pulmonary hypertension (PH)

1. PAH
   - IPAH
   - FPAH
   - APAH
     - Collagen vascular disease
     - Congenital systemic-to-pulmonary shunts[#]
     - Portal hypertension
     - HIV infection
     - Drugs and toxins
     - Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
   - Associated with signicant venous or capillary involvement
     - PVOD
     - PCH
   - Persistent PH of the newborn
2. PH with left heart disease
   - Left-sided atrial or ventricular heart disease
   - Left-sided valvular heart disease
3. PH associated with lung diseases and/or hypoxaemia
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Sleep disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities
4. PH due to chronic thrombotic and/or embolic disease
   - Thromboembolic obstruction of proximal pulmonary arteries
   - Thromboembolic obstruction of distal pulmonary arteries
   - Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
5. Miscellaneous
   - Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

The revised clinical classification of PH was proposed in 2003 at the 3rd World Symposium on Pulmonary Hypertension in Venice (Italy). PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; FPAH: familial PAH; APAH: associated PAH; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary heamangiomatosis. [#]: guidelines for classification of congenital systemic-to-pulmonary shunts are presented in table 3. Reproduced and modified from [63] with permission from the publisher.

It was decided that the general format of the Evian classification should be retained during the 4th World Symposium held in 2008 [64]. PAH includes patients with a family history of IPAH who also have germline mutations. In the subgroup of PAH, the patients with schistosomiasis and chronic haemolytic anaemia were added as separate entities. PVOD and pulmonary capillary haemangiomatosis (PCH) were now included as distinct from Group 1, and the group was renamed Group 1′. As a result, Group 1 of the PAH subgroup was both associated with successful therapy and became a more homogeneous group.

There followed a review and update of the ERS/ESC guidelines in 2009 [61].

## The molecular mechanisms of vascular remodelling in PH

Let us consider familial PAH, which makes up around 6–18% of IPAH patients. Familial PAH was initially defined as those with more than one affected family member. The alternative term for this is heritable IPAH. As with IPAH, the illness is amenable to treatment.

### Genetics of familial PAH

An autosomal-dominant pattern of inheritance with reduced penetrance has previously been demonstrated in segregation studies [65]. Two studies performed independently reported heterozygous germline mutations in the BMPR II of families with PAH [66, 67]. These mutations have been found in approximately 80% of familial PAH cases.

It is particularly interesting to note that PAH patients with no family history also harbour *BMPR*2 mutations; this is seen in 11–40% of cases [68]. The mechanism of the disease being the result of the first genetic abnormality converted to a disease phenotype by a "second hit" was proposed to account for the reduced penetrance in families with PAH. Additional hits might include inflammatory insults or the increased activity of a vasoconstrictor factor; serotonin, for example [69]. The deficiency of BMPR function may be further compounded by such "second hits", as they may alter receptor expression, downstream signalling or gene transcription.

**Table 3.** Guidelines for classification of congenital systemic-to-pulmonary shunts

1. Type
   - Simple
     - ASD
     - VSD
     - Patent ductus arteriosus
     - Total or partial unobstructed anomalous pulmonary venous return
   - Combined
     - Describe combination and define prevalent defect if any
   - Complex
     - Truncus arteriosus
     - Single ventricle with unobstructed pulmonary blood flow
     - Atrioventricular septal defects
2. Dimensions
   - Small: ASD 2.0 cm and VSD 1.0 cm
   - Large: ASD 2.0 cm and VSD 1.0 cm
3. Associated extracardiac abnormalities
4. Correction status
   - Noncorrected
   - Partially corrected (age)
   - Corrected: spontaneously or surgically (age)

ASD: atrial septal defect; VSD: ventricular septal defect. Reproduced and modified from [63] with permission from the publisher.

Dysfunctional BMPR signalling is also seen in IPAH; BMPR II protein expression is reduced in the lungs of patients with no detectable mutation in BMPR II [70]. Experimental PH in rats induced by monocrotaline has shown reduced expression of BMPR II [71]. This suggests that a critical reduction in the expression of BMPR II or a reduction in BMPR II signalling is a cause of PAH, whether or not there is a mutation in the *BMPR2* gene.

BMPR II signalling, like other type II receptor members of the transforming growth factor (TGF)-β superfamily, is a constitutively active serine threonine receptor kinase [72]. The type II receptor activates an associated type I receptor (BMPR-1A (or activin receptor-like kinase (ALK)-3) or BMPR-1B (or ALK-60) in the presence of ligands (BMPs 2, 4, 6, 7

and 9, and growth differentiation factors) [72, 73]. The type I receptor is phosphorylated by the downstream signalling molecules Smads 1, 5 and 8. BMP9 has been recognised as a ligand for a receptor complex that is comprised of BMPR-II and ALK-1, establishing a link between PAH and hereditary haemorrhagic telangiectasia (HHT)[74]. Mutations in the ALK-1 have been noted in patients with type 2 HHT; interestingly, they have also been identified in patients with severe PAH [75].

Changes in the control of BMP-regulated genes in pulmonary vascular smooth muscle and endothelial cells are believed to predispose patients to pulmonary vascular remodelling development. Many of the mutations in BMPR II (approximately 70%) are either nonsense or frameshift mutations, and these are likely to result in the transcript being degraded by nonsense-mediated messenger RNA decay. Thus, only the non-mutant allele results in the production of protein, leading to a state of haplo-insufficiency [72]. About 30% of mutations lead to missense mutations in highly conserved amino acids in functional domains of the receptor. Some of these interrupt trafficking of the receptor to the cell surface [76]. Kinase domain mutations lead to a failure to activate the type I receptor. Missense mutations also occur in the long cytoplasmic tail of BMPR II. Studies in cells from patients harbouring mutations in BMPR II demonstrate that all mutations lead to a reduced capacity for Smad phosphorylation and the reduced transcription of BMP target genes [77]. BMPR II mutations cause a reduction in BMP-mediated function, affecting growth, migration and differentiation.

As we have seen, there is a parallel disease in which missense mutations lead to reduced trafficking to the cell surface: CF. Here, small molecule therapy has been developed, which improves lung function in patients with disease. This may provide a similar opportunity to treat the various genotype-linked phenotypes of heritable PAH.

### The platelet-derived growth factor pathway

Platelet-derived growth factors (PDGF) have emerged as an important mechanism of PAH. Hypoxia, for example, experimentally induces increased expression of PDGF-A and PDGF-B isoforms [78], and PDGF-A is overexpressed in the lungs of patients with severe PAH [79]. PDGF may contribute to pulmonary vascular remodelling *via* several mechanisms: it is a potent mitogen, it increases cell migration and it increases extracellular matrix deposition [80, 81]. PDGF potently inhibits apoptosis in vascular smooth muscle cells.

A tyrosine kinase inhibitor (TKI) called imatinib, which was approved as a treatment for chronic myeloid leukaemia, was studied in PAH based on a clever set of observations on the role of tyrosine kinase in experimental pulmonary artery disease [81, 82]. Imatinib is a small molecular inhibitor of the tyrosine kinases, which blocks the actions of PDGF receptors as well as other kinases. This experimental work used monocrotaline-induced PH in rats and hypoxic PH in mice; imatinib was shown to significantly reduce $P_{pa}$. The work was translated to a study of a single patient who showed a marked improvement in 6MWD. The work was extended to two further successful cases [83]. A randomised controlled study then confirmed the findings [84].

Development of new approaches to PAH TGF-β-driven responses, or the enhancement of BMP signalling, may provide therapies that target dysfunctional cellular signalling, driving the processes involved in pulmonary vascular remodelling.

## Pulmonary vascular disease seen from a historical perspective

We have seen how successive steps in clinical observation, the introduction of physiological measurements, epidemiology, genetic analysis revealing mutations of genes in a common pathway, and detailed work on remodelling of pulmonary vasculature have led to promising new therapies and a way of reversing the disease. As previously discussed, an enormous debt for this revolution in care is owed to the dedicated physicians, surgeons, pathologists and scientists, not to mention the courageous patients.

### *Statement of Interest*

T. Higenbottam has acted as an expert witness in primary pulmonary hypertension fenfluramine cases. He is also a Senior Partner of Transcrip Partners.

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# Chapter 2

# Pulmonary hypertension: diagnosis, differential diagnosis and pitfalls

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**SUMMARY: Pulmonary hypertension (PH) is a haemodynamic state that can be encountered in many different diseases. Sometimes, PH is caused by characteristic changes in small pulmonary arteries and treatment with pulmonary-specific vasodilators is indicated only in those cases (classified as pulmonary arterial hypertension (PAH)). In other conditions associated with PH, these treatments can be dangerous and alternative therapeutic approaches may be required. Because the choice of treatment is critically dependent on a correct classification of the disease, updated European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines provide a systematic roadmap for the diagnosis of PH. Even with these guidelines, it can sometimes still be difficult to come to the right conclusion. In this chapter, we illustrate the diagnostic pitfalls using clinical cases from the Pulmonary Hypertension Center at the VU University Medical Center (Amsterdam, the Netherlands).**

**KEYWORDS: Diagnostic algorithm, differential diagnosis, pulmonary arterial hypertension, pulmonary hypertension, treatment, World Health Organization classification**

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Determining the cause of pulmonary hypertension (PH) is complex and requires a structured and interdisciplinary approach. Because it is the basis of decisions for treatment, a precise diagnosis is obligatory. Table 1 summarises the known causes of PH adapted from the world conference on PH held in Dana Point, CA, USA [1]. The table shows that all diagnoses can be divided into five main categories. The first category is termed pulmonary arterial hypertension (PAH) and includes a broad variety of possible causes of PH characterised by the same pattern of vascular remodelling. World Health Organization (WHO) group 1 PAH patients are most likely to respond to PAH-specific therapy. Therefore, although this group represents less common causes of PH, a correct diagnosis of this group is of utmost importance. The second category consists of PH due to left heart disease. The third category represents PH associated with parenchymal lung disease and/or hypoxia. The fourth category consists of chronic thromboembolic pulmonary hypertension (CTEPH): nonresolution of acute embolic masses that later undergo fibrosis leading

to mechanical obstruction of the pulmonary vasculature. Since surgery can offer a cure, accurate imaging of the pulmonary vasculature to assess operability is important in CTEPH. The fifth group is ''miscellaneous'': it contains many inflammatory diseases that may directly affect the arteriolar wall. The diagnostic approach used in this chapter is adapted from the European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines on PH [2]. Since these guidelines provide an excellent overview, the purpose of this chapter is to briefly summarise the diagnostic steps and focus on the differential diagnosis and diagnostic pitfalls that can appear when making a diagnosis of PH.

## Making the diagnosis of PH

In diagnosing PH, we must first consider that it is not a disease but a haemodynamic condition with a mean pulmonary artery pressure ($P_{pa}$) of over 25 mmHg. In the past, a mean $P_{pa}$ over 30 mmHg during exercise was used to define PH. However, since recent research revealed that half of people older than 50 years of age show a mean $P_{pa}$ of over 30 mmHg during mild exercise, this elevation in mean $P_{pa}$ is no longer used to define PH [3]. Symptoms are largely nonspecific. However, all causes of PH share an impairment of right ventricular (RV) function due to an increased afterload. The ensuing limitation in cardiac output first becomes overt during exercise. For this reason, the most common symptoms of PH are exercise intolerance and fatigue. Other

**Table 1.** Classification of pulmonary hypertension

**1 Pulmonary arterial hypertension**
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 Bone morphogenetic protein receptor type II
  - 1.2.2 Activin receptor-like kinase 1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drug and toxin induced
- 1.4 Associated pulmonary arterial hypertension
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

**1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**

**2 Pulmonary hypertension due to left heart disease**
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

**3 Pulmonary hypertension due to lung diseases and/or hypoxia**
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

**4 Chronic thromboembolic pulmonary hypertension**

**5 Pulmonary hypertension with unclear and/or multifactorial mechanisms**
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorder: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

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frequent symptoms related to the overloaded RV are palpitations and chest pain. Symptoms of RV failure, such as ankle oedema and ascites, occur late in the disease.

PH is frequently discovered by chance when typical signs are seen during a physical examination or diagnostic testing, including ECG, chest radiography or Doppler echocardiography. A typical example of an abnormal radiograph is given in figure 1.

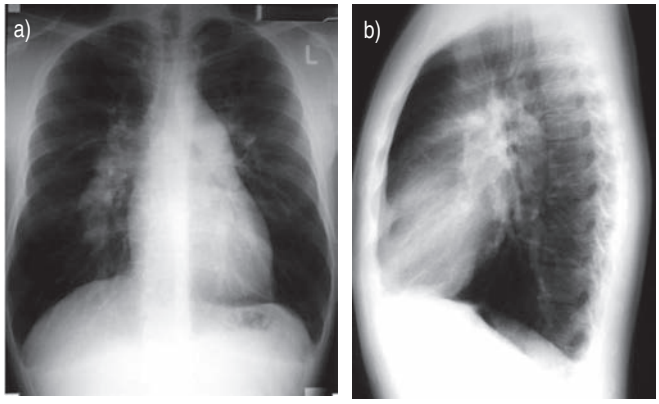


**Figure 1.** Radiograph of a patient with pulmonary hypertension showing dilated pulmonary arteries and right ventricular enlargement (a), also visible as a filling of the retrosternal space on the lateral view (b).

Finally, the diagnosis can be made if screening is performed in groups at high risk for the development of PAH, such as carriers of mutations in the bone morphogenetic protein receptor type II (*BMPR2*) gene, patients with connective tissue disease (CTD), patients with liver diseases and HIV patients.

### Pitfall: false-positive echocardiography in high output state

Doppler echocardiography is a frequently used screening tool for PH in high-risk populations. This technique allows estimation of the systolic $P_{pa}$ ($sP_{pa}$) by determining right atrial pressure ($P_{ra}$) and the tricuspid regurgitant jet velocity (TRJV). Based on the Bernoulli equation, $sP_{pa}$ is calculated as $P_{ra}+(4 \times TRJV^2)$. After an initial report of a significantly increased mortality in sickle cell patients with a TRJV greater than 2.5 $m \cdot s^{-1}$ [4], this group of patients was the focus of a lot of attention and clinical trials were designed to evaluate the use of PAH-specific medication. PH in sickle cell disease is multifactorial; however, only the performance of a right heart catheterisation (RHC) allows correct assessment of the diagnosis. It was recently shown that an elevated TRJV in sickle cell disease is only rarely associated with an elevated pulmonary vascular resistance (PVR). Much more common causes of an elevated TRJV in sickle cell disease are a hyperdynamic circulation (due to low haemoglobin levels) and left heart disease [5]. Other examples of high output states leading to an elevated TRJV despite a normal PVR are hyperthyroidism, the presence of an arterial venous shunt and the hepatopulmonary syndrome. In summary, an elevated TRJV can be a sign of PAH but is also found in many other diseases.

## The diagnostic work-up: frequent causes first

After the suspicion is raised that PH is present, which at least requires an ultrasound, further diagnostic work-up is warranted. Although PH can only be confirmed by means of a RHC, this test is only mandatory when therapeutic consequences are expected. For this reason, the diagnostic work-up does not start with performing a RHC, but with the exclusion of the most

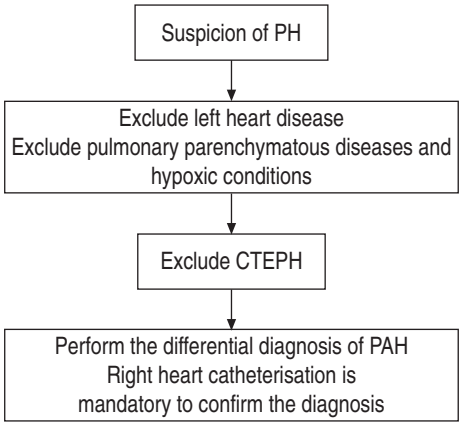
Suspicion of PH
Exclude left heart disease
Exclude pulmonary parenchymatous diseases and hypoxic conditions
Exclude CTEPH
Perform the differential diagnosis of PAH
Right heart catheterisation is mandatory to confirm the diagnosis

**Figure 2.** A simplified diagnostic algorithm for the diagnosis of pulmonary hypertension (PH) derived from the European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines on pulmonary arterial hypertension (PAH) [2]. CTEPH: chronic thromboembolic pulmonary hypertension.

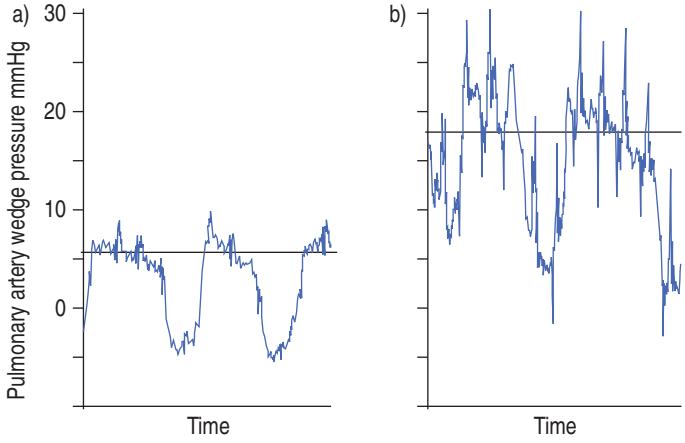


**Figure 3.** a) Optimal measurement of pulmonary artery wedge pressure must be performed at the last complete pressure wave at end-expiration before the onset of inspiration. Automated software usually averages the entire data set, therefore manual determination of the pulmonary capillary wedge pressure is mandatory. b) Patients with diastolic heart failure may have normal wedge pressure if taking maximal diuretics. After a fluid challenge, the abnormal rise of wedge pressure can be noted. The horizontal line in both panels is the correct wedge pressure after manual adjustment.

common causes of PH, represented by WHO groups 2 and 3. The adapted diagnostic algorithm of the ERS/ESC guidelines for the diagnosis and treatment of PH is shown in figure 2.

## Diagnosing PH due to left heart disease

Because left heart failure is characterised by increased filling pressures of the left ventricle (LV), the most characteristic hallmark of this disease is an increased wedge pressure. However, in most cases of overt valvular heart failure and systolic left heart failure, echocardiography will suffice. Perhaps the most difficult cause of PH to diagnose is PH secondary to diastolic heart failure (heart failure with preserved ejection fraction (HFPEF)). Clinical features that should raise suspicion of HFPEF are older age, obesity and a history of diabetes mellitus, atrial fibrillation or systemic hypertension. Signs of LV hypertrophy on ECG and an enlarged left atrium on echocardiography further increase the likelihood of this diagnosis. Although more advanced cardiac ultrasound techniques, such as strain imaging and determination of Doppler parameters of diastolic heart failure, frequently allow diagnosis of this disease, a right or left heart catheterisation is still required in many patients. In the current guidelines, a pulmonary artery wedge pressure or LV end-diastolic pressure greater than 15 mmHg is used to discriminate between pre-capillary (15 mmHg or lower) and post-capillary (more than 15 mmHg) PH. Given the decisive nature of wedge pressure in these cases, its accurate measurement is of paramount importance. Although in the past, excellent relationships between wedge pressures and LV end-diastolic pressures have been described, more recent reports challenge the accuracy of wedge pressure as a surrogate for LV end-diastolic pressure [6]. Methodological errors may underlie the inaccuracy. An example is given in figure 3.

In addition, fluid volume conditions directly affect LV filling pressures and, therefore, wedge pressures. A patient with PH secondary to left heart failure may exhibit normal wedge pressures after appropriate or too vigorous treatment with diuretics. Withdrawal of diuretics and fluid loading may be required during heart catheterisation to determine the correct diagnosis. A standardised protocol and criteria for volume loading do not exist.

*A 38-year-old male who first tested HIV positive 4 years ago was not treated with antiretroviral therapy because of a normal CD4 count and undetectable HIV RNA. After he presented with symptoms of shortness of breath, echocardiography showed signs of PH together with an abnormal contraction pattern of both ventricles. Based on the echocardiogram, a presumptive diagnosis was made of HIV-related cardiomyopathy and PH secondary to left heart failure. Despite antiretroviral therapy, the patient developed clinical signs of overt RV failure and was referred to the VU Medical Center (Amsterdam, the Netherlands). Repeated echocardiography showed worsening of PH, a poor RV function and, again, an abnormal contraction pattern of the LV. No other causes of PH were found.*

*The patient's dyspnoea had deteriorated to New York Heart Association (NYHA) class IV. To distinguish between cardiomyopathy-associated PH and HIV-associated PAH, a RHC was performed, showing a mean $P_{pa}$ of 35 mmHg, a mean $P_{ra}$ of 29 mmHg, a mixed-venous oxygen saturation of 36%, a cardiac output of 2.0 $L \cdot min^{-1}$, a PVR of 1,120 $dyn \cdot s \cdot cm^{-5}$ and a wedge pressure of 7 mmHg. Systemic blood pressure was 74/57 mmHg. These haemodynamic data were compatible with a diagnosis of HIV-associated PAH. While the echocardiogram suggested a concurrent diagnosis of cardiomyopathy, the low wedge pressure proved a pre-capillary origin of the existing PH. The patient was treated with an endothelin receptor antagonist (ERA) while his HIV medication was continued, and this resulted in a dramatic clinical improvement (NYHA class I). Although PH secondary to left heart failure is commonly misdiagnosed as PAH (this occurs particularly in cases of HFPEF), the opposite also occurs. Especially in patients with systemic lupus erythematosus (SLE) and HIV-associated PAH, some type of cardiomyopathy can exist together with PAH. In those cases, only a RHC can distinguish between pre- and post-capillary PH. This case not only illustrates the difficulty in distinguishing PAH from pulmonary venous hypertension, but also that HIV-associated PAH can occur in the context of a low infectious burden.*

## Diagnosing PH due to hypoxic or pulmonary disease

Another frequent cause of PH is hypoxic or pulmonary disease. The most commonly encountered difficulty in the diagnosis of this disease is whether the diagnosis of a lung disease is a sufficient explanation for the presence and degree of PH. An integrated interpretation of all pulmonary function tests and a thorough understanding of the epidemiology of the different lung diseases are necessary to determine whether a certain degree of PH is ''in proportion'' to the severity of the underlying pulmonary disease. For instance, chronic obstructive pulmonary disease (COPD) can cause PH but the observation of a mean $P_{pa}$ greater than 40 mmHg in a normoxic COPD patient with mild airflow obstruction is very unusual [7]. In such cases, further diagnostic steps are required, and pulmonary embolism will have to be excluded first. However, if after a review of the high-resolution computed tomography (HRCT) images, the diagnosis is changed to histiocytosis X, the existence of a chronic lung disease may well explain the degree of PH [8]. PAH occasionally mimics chronic lung disease when PH is found in a hypoxaemic patient with a very low diffusion capacity, normal spirometry and the absence of abnormalities on HRCT imaging.

*A 48-year-old patient who had never smoked was referred to our hospital for the evaluation of PH. Her past medical history included a patent ductus Botalli closed at the age of 4 years and a diagnosis of COPD based on spirometric criteria. In the years before admission, she experienced progressive exercise intolerance, despite unchanged spirometric values. On evaluation, reopening of the ductus was excluded by means of magnetic resonance imaging (MRI). RHC performed at the VU Medical Center revealed a mean $P_{pa}$ of 45 mmHg, a wedge pressure of 9 mmHg and a PVR of 653 $dyn \cdot s \cdot cm^{-5}$. Chronic thromboembolic disease was excluded by means of computed tomography angiography and ventilation/perfusion scintigraphy. Although the HRCT shown in figure 4 may suggest some degree of emphysema (visible as hyperlucent lung areas), the segmental and lobar appearance of the hyperlucency together with the*

**Figure 4.** High-resolution computed tomography of the lungs of a 48-year-old never-smoker referred for evaluation of pulmonary hypertension, showing hyperlucency and dilated pulmonary arterial vessels compressing the airways.

**Figure 5.** High-resolution computed tomography of a 16-year-old male with pulmonary capillary haemangiomatosis, showing pleural fluid, paraseptal lining and ground-glass opacities of the lung. Wedge pressure was 7 mmHg.

*widely enlarged pulmonary arteries compressing the airways show that the hyperlucency is the consequence of air trapping in regions with airways almost completely obstructed by large pulmonary vessels. Likewise, the obstructive lung pattern was the consequence of partial airway obstruction due to vascular compression. A diagnosis of PAH was made, probably relating to a late closure of a patent ductus. Compression of the airways by enlarged pulmonary arteries can be encountered in PAH and can lead to various types of airway obstruction. The pitfall is not to misclassify those patients as having severe asthma or COPD* [9].

A low diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) is present in 10% of patients with PAH [10] and is associated with a poor prognosis [11]. However, the presence of low $D_{L,CO}$ should always raise the suspicion of an alternative diagnosis. First, low $D_{L,CO}$ may indicate an undiagnosed parenchymal lung disease. Interstitial lung diseases that can be associated with out-of-proportion PH are extrinsic allergic alveolitis, lymphocytic interstitial pneumonitis, amyloidosis and sarcoidosis. Although it is not always clear in those cases whether the underlying pulmonary disease explains the (degree of) PH, all these diagnoses are characterised by low $D_{L,CO}$. In addition, low $D_{L,CO}$ can be present in PH secondary to left heart failure. After exclusion of underlying lung and heart diseases, a diagnosis of pulmonary veno-occlusive disease (PVOD) or pulmonary capillary haemangiomatosis (PCH) should be considered. Although only a histopathological examination can confirm this diagnosis, obtaining a surgical lung biopsy carries a high risk. For this reason, a noninvasive diagnosis based on clinical characteristics is justified [12]. In particular, HRCT can be of great help to establish a diagnosis of PVOD. Characteristics of PVOD on chest HRCT are centrilobular ground-glass opacities, septal lines, mediastinal lymphadenopathy and pleural effusion; HRCT characteristics of PCH are diffuse bilateral thickening of the interlobular septa and the presence of small, centrilobular, poorly circumscribed nodular opacities [13]. In idiopathic PAH (IPAH) and PVOD, the ventilation/perfusion scan may show small peripheral unmatched and nonsegmental perfusion defects, but this is not usually the case [14]. Finally, the presence of haemosiderophages in the bronchial alveolar lavage fluid may provide additional clinical evidence to suggest a diagnosis of PVOD. PAH related to CTD is another important entity in the differential diagnosis of PAH with low $D_{L,CO}$, including SLE, rheumatoid arthritis, scleroderma, Sjögren's syndrome and mixed connective tissue disease (MCTD). Of these, scleroderma has the highest prevalence of PAH.

**Figure 6.** Computed tomography image of an angiosarcoma. The right main pulmonary artery is occluded by a large bulging process. No other central or peripheral occlusions are seen. The chance of such a massive pulmonary embolism without emboli elsewhere in the lung is very low, making the diagnosis of a rare disease such as sarcoma more likely. The endovascular lesion was positron emission tomography positive (although large thrombi have also occasionally been described as positive). Angiography showed its limitation to 2 cm within the two branches. The tumour was successfully removed by pneumectomy without recurrence in 5 years.

*A 16-year-old male, who had been treated for 5 years because of a presumed diagnosis of asthma, was referred by his paediatrician because of presence*

*of severe PH on echocardiography. He had NYHA class IV symptoms of dyspnoea and his oxygen saturation was 85% with 5 L oxygen per minute. Pulmonary emboli and left sided heart disease were ruled out. A RHC revealed a mean* $P_{ra}$ *of 11 mmHg, a mean* $P_{pa}$ *of 80 mmHg and a wedge pressure of 7 mmHg without reversibility on nitric oxide (NO). The HRCT scan showed a typical pattern of PVOD or PCH (fig. 5).*

*He was kept on mild doses of epoprostenol and listed for urgent lung transplant. After a period of being seemingly stable, he died suddenly 4 weeks after the start of treatment.* Post mortem *investigation showed a recently infarcted RV and PCH.*

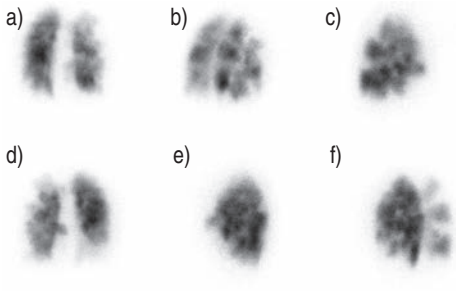


**Figure 7.** Perfusion scintigraphy of a 70-year-old female with progressive shortness of breath and exercise intolerance. a) Posterior perfusion, b) right posterior oblique, c) right lung perfusion, d) anterior perfusion, e) left lung perfusion and f) left posterior oblique perfusion.

## Chronic thromboembolic pulmonary hypertension

After exclusion of pulmonary or cardiac diseases, the next step in the diagnostic work-up is to exclude CTEPH. According to the guidelines, ventilation/perfusion imaging is still obligatory for this diagnosis. This is because chronic thromboembolic disease can be easily missed on computed tomography angiography, especially when the radiologist is inexperienced. Invasive measurement of the $P_{pa}$ is necessary to confirm a diagnosis of CTEPH. The pressure measurements can be combined with pulmonary angiography into one session. Pulmonary angiography is still the gold standard for the evaluation of peripheral vascular lesions. An important differential diagnosis to CTEPH is angiosarcoma. An example is given in figure 6. The level of clinical suspicion should be raised if a lobulated mass is visible centrally in the pulmonary artery. In addition, MRI can differentiate a tumour mass from a thrombus [15]. Fluorodeoxyglucose uptake in the lesion measured by means of positron emission tomography (PET) can further support the diagnosis.

*A 70-year-old female experienced progressive shortness of breath and exercise intolerance. Although she had no history of thromboembolism, her daughter and sister had been diagnosed with deep vein thrombosis. A ventilation/perfusion scan was highly suggestive of pulmonary embolism (fig. 7). The computed tomography angiography, however, did not show central pulmonary emboli. In addition, the patient did not improve on anticoagulation therapy (warfarin), for which reason, she was referred to our hospital. A combined RHC and pulmonary angiography was performed. RHC revealed a mean* $P_{pa}$ *of 38 mmHg, mixed-venous saturation of 80%, cardiac output of 6.1* $L \cdot min^{-1}$ *(direct Fick) and PVR of 380* $dyn \cdot s \cdot cm^{-5}$*. The pulmonary angiography did not show any signs of pulmonary embolism. In the venous phase of the contrast, an aberrant pulmonary venous connection was detected between the left upper lobe pulmonary vein and the left subclavian vein (fig. 8). For this reason, a diagnosis of PAH related to a systemic to pulmonary shunt was made. The possibility of false-positive perfusion scans in congenital heart–lung disease is well known* [16].

## The differential diagnosis of PAH

Finally, after exclusion of all previously discussed causes, one arrives at the PAH group. Although many disease conditions can lead to PAH, the commonality between all causes is a similar type of remodelling of the pulmonary vascular bed and a response to PAH-specific medication. Careful history taking and additional tests are required to search for one of the underlying causes mentioned in table 1. If none is found, the diagnosis is idiopathic or heritable. For

**Figure 8.** Venous phase of the pulmonary angiography of a 70-year-old female with progressive shortness of breath and exercise intolerance, showing the aberrant connection between the left upper lobe vein and the left subclavian vein (arrow).

the diagnosis of PAH, RHC and reversibility testing using NO inhalation and prostacyclin infusion are obligatory. A minority of PAH patients will appear to be vasoreactive, defined as a reduction in $P_{pa}$ of 10 mmHg or more to reach an absolute value of $P_{pa}$ of 40 mmHg or less with an increased or unchanged cardiac output [17]. Many of those patients are long-term responders to calcium channel blocker (CCB) therapy. Although the interpretation of all tests mentioned above may seem straightforward, outcomes should be interpreted carefully. This is especially true when considering the data provided by RHC. It may become necessary to revise a previously established diagnosis, as is exemplified in the following case study [18].

*A 31-year-old male presented with symptoms of dyspnoea on exertion and one occasion of haemoptysis. He was a previously healthy non-smoker who regularly exercised and never used drugs or alcohol. On physical examination, a loud second heart sound was noted and the ECG showed right-axis deviation. Chest radiography and computed tomography showed enlargement of the heart and pulmonary vessels, but no other abnormalities. Cardiac ultrasound showed RV hypertrophy, but because no tricuspid regurgitant jet was observed, $sP_{pa}$ could not be estimated. RHC revealed a mean $P_{pa}$ of 50 mmHg, a normal wedge pressure and a high cardiac output of 10.1 $L \cdot min^{-1}$. Because of this hyperdynamic circulation, a liver disorder or portosystemic shunt was suspected. A vascular MRI indeed showed a persistent ductus venosus directly connecting the portal vein with the vena cava. Therefore, a diagnosis of PAH due to an Abernethy malformation was made.*

## Conclusion

A correct diagnosis in PH is of great clinical importance. Although the current algorithm [2] provides an excellent structure for using the available tests to diagnose PH, the case studies we have presented here show that the diagnosis is, even then, a challenge. It is the art of medicine to arrive at a correct diagnosis, by using an integral interpretation of the symptoms of the patients, underlying conditions and results of each of the diagnostic tests; for this, experience and a multidisciplinary approach are mandatory.

### *Statement of Interest*

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# Chapter 3

# Current medical therapies in pulmonary arterial hypertension

*Nazzareno Galiè, Alessandra Manes and Massimiliano Palazzini*

**SUMMARY: The progress made in the medical treatment of pulmonary arterial hypertension (PAH) in the past 15 years is unique, particularly for a rare and severe condition. To date, seven drugs belonging to three pharmacological classes (endothelin receptor antagonists (ERA), phosphodiesterase type-5 inhibitors (PDE-5 I) and prostanoids) administered by four different routes (oral, inhaled, subcutaneous and intravenous) have been approved by the Food and Drug Administration and the European Medicines Agency. All three classes of drug exert both vasodilator and antiproliferative effects, and interfere with the endothelial dysfunction abnormalities observed in PAH patients. Modern drug therapy, including combination therapy, leads to a significant improvement in PAH patients' symptomatic status and a slower rate of clinical deterioration. Despite this finding, PAH remains a chronic disease without a cure. In addition, the medical and interventional treatments for more advanced cases are still invasive and prone to significant side-effects. Future candidate compounds on phase III drug development are as follows: macitentan, a novel dual ERA with tissue penetration properties; selexipag, an orally available selective prostacyclin receptor agonist; riociguat, a soluble guanylate cyclase stimulator; and imatinib, a tyrosine kinase inhibitor.**

**KEYWORDS: Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostanoids, pulmonary arterial hypertension, pulmonary hypertension**

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Pulmonary arterial hypertension (PAH) is a rare and severe clinical condition characterised by a progressive increase of pulmonary vascular resistance (PVR) leading to right ventricular (RV) failure and premature death [1]. PAH prevalence ranges from 15 to 50 per 1 million-patient population [2, 3] and it affects relatively young patients (average age 50 years). PAH in adults includes at least nine clinical subgroups with virtually identical obstructive pathological changes in the distal pulmonary arteries: idiopathic PAH (IPAH), heritable PAH, drug- and toxin-induced

PAH, associated PAH (APAH), connective tissue diseases (CTD), HIV infection, portal hypertension, congenital heart disease (CHD), schistosomiasis, and chronic haemolytic anaemia [1].

Two decades ago, patients with IPAH were defined as being in the "kingdom of the near-dead" [4] to outline their dismal median survival rate; at that time, it was 2.8 years after diagnosis [5], despite any available supportive treatment. Doubtless, the progress made in the medical treatment of PAH in the past 15 years is unique, particularly for a rare and severe condition: almost 30 randomised controlled trials have been completed and more than 10 are either ongoing or planned. 28 randomised controlled trials have been published as of May 2012. Seven drugs belonging to three pharmacological classes (endothelin receptor antagonists (ERAs), phosphodiesterase type-5 inhibitors (PDE-5 I) and prostanoids) administered by four different routes (oral, inhaled, subcutaneous and intravenous) have currently been approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA). All three classes of drug exert both vasodilator and antiproliferative effects, and interfere with the endothelial dysfunction abnormalities observed in PAH patients [6].

Modern drug therapy leads to a significant improvement in PAH patients' symptomatic status and a slower rate of clinical deterioration. In addition, different meta-analyses performed in randomised controlled trials in PAH patients [7–9] have shown a reduction in mortality ranging 38–44%, and a 61% reduction in hospitalisations [7] in patients treated with targeted therapies *versus* patients randomised to placebo. These results, achieved after an average treatment period of 14.3 weeks, support the efficacy of the currently approved PAH treatments. Despite this finding, PAH remains a chronic disease without a cure. In addition, the medical and interventional treatments for more advanced cases are still invasive and prone to significant side-effects.

## Medical therapy

The therapy of PAH patients cannot be considered as a mere prescription of drugs but is characterised by a complex strategy that includes: the evaluation of severity, general and supportive measures, the assessment of vasoreactivity, the estimation of efficacy and the combination of different drugs plus interventions. In any of these steps, the knowledge and experience of the physician responsible are critical to optimise available resources.

## General measures

General measures include recommendations on physical activity, pregnancy and birth control, air travel, psychological support, infection prevention and elective surgery.

### Physical activity and supervised rehabilitation

Patients should avoid excessive physical activity that leads to distressing symptoms, but they should be encouraged to be active within symptom limits. When physically deconditioned, they may undertake supervised exercise rehabilitation. One study has demonstrated an improvement in exercise capacity in patients with PAH who took part in a training programme [10]. More data are required before specific recommendations can be made.

### Pregnancy and birth control

Pregnancy is associated with 16–30% mortality in patients with PAH [11, 12], despite current treatments; as a consequence, PAH is a contra-indication to pregnancy. Barrier contraceptive methods are safe but with an unpredictable effect. Progesterone-only preparations, such as medroxyprogesterone acetate and etonogestrel, are effective approaches to contraception and avoid the potential issues of oestrogens [13]. It should be remembered that the ERA bosentan may reduce the efficacy of oral contraceptive agents. The Mirena® coil (Bayer AG, Leverkusen, Germany) is also effective but, in rare cases, leads to a vasovagal reaction when inserted, which may be poorly tolerated

in severe PAH [13]. A combination of two methods may also be utilised. The patient who becomes pregnant should be informed of the high risk of pregnancy and termination of pregnancy should be discussed. Those patients who choose to continue pregnancy should be treated with disease-targeted therapies, and there should be planned elective delivery and effective close collaboration between the obstetricians and the PAH team [14, 15].

### Air travel

Flight oxygen administration should be considered for patients in World Health Organization (WHO)/New York Heart Association (NYHA) functional classes III and IV, and in those with an arterial oxygen saturation ($S_{a,O_2}$) of <92%. A flow rate of 2 L·min$^{-1}$ will raise inspired oxygen pressure to values seen at sea level. Similarly, such patients should avoid going to altitudes above 1,500–2,000 m without supplemental oxygen.

### Psychosocial support

Many PAH patients develop anxiety and depression leading to impairment in quality of life. Timely referral to psychiatrists or psychologists should be made when appropriate.

### Infection prevention

Patients with PAH are susceptible to developing pneumonia, which is the cause of death in 7% of cases. While there are no controlled trials, it is sensible to recommend vaccination against influenza and pneumococcal pneumonia.

### Elective surgery

Elective surgery is expected to have an increased risk in patients with PAH. It is not clear which form of anaesthesia is preferable but epidural is probably better tolerated than general anaesthesia. Patients usually maintained on oral therapy may require temporary conversion to *i.v.* or nebulised treatment until they are able to both swallow and absorb drugs taken orally.

## Supportive therapy

Supportive therapy includes oral anticoagulant treatment, diuretics, oxygen therapy, and digoxin and other inotropic drugs.

### Oral anticoagulant treatment

The evidence for the favourable effects of oral anticoagulant treatment in patients with IPAH or PAH associated with the use of anorexigens, is based on retrospective analysis of single-centre studies [16, 17]. The target international normalised ratio (INR) in patients with IPAH varies somewhat, at 1.5–2.5 in most centres in North America and 2.0–3.0 in European centres. The evidence supporting anticoagulation in patients with IPAH may be extrapolated to other patients with PAH, providing that the risk/benefit ratio is carefully considered in the presence risks factors for bleeding, particularly in patients with porto-pulmonary hypertension (POPH) or CTDs (in the presence of gastro-intestinal tract abnormalities). Generally, patients with PAH receiving therapy with long-term *i.v.* prostaglandins (PGs) are anticoagulated in the absence of contra-indications, which is partly due to the additional risk of catheter-associated thrombosis.

### Diuretics

Patients with decompensated right heart failure develop fluid retention that leads to increased central venous pressure, abdominal organ congestion, peripheral oedema and, in advanced cases,

ascites. Appropriate diuretic treatment in right heart failure, either *i.v.* (in acute decompensation) or oral, offers clear symptomatic and clinical benefits in patients with PAH. High doses of oral diuretics may be required in cases of reduced intestinal absorption. The addition of aldosterone antagonists should also be considered.

### Oxygen

No consistent data are currently available on the effects of long-term oxygen treatment in PAH. Although improvement in pulmonary hypertension (PH) with low-flow supplemental oxygen has been reported in some PAH patients, this has not been confirmed in controlled studies. However, it is generally considered important to maintain $S_{a,O_2}$ at greater than 92% at all times. Ambulatory oxygen may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.

### Digoxin and other inotropic drugs

Digoxin has been shown to improve cardiac output acutely in IPAH, although its efficacy is unknown when administered chronically [18]. It may be given to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias. Patients with end-stage PAH are treated with *i.v.* dobutamine in most expert centres [19].

## Specific drug therapy

In this section, we will consider treatment with calcium channel blockers (CCBs) in vasoreactive patients and treatment with the more recently developed classes of drugs (ERAs, PDE-5 I and prostanoids). An updated list of drug–drug interactions is reported in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines on the diagnosis and treatment of PH [1].

### Calcium channel blockers

Smooth muscle cell hypertrophy, hyperplasia and vasoconstriction have long been known to contribute to the pathogenesis of IPAH, and this has led to the use of traditional vasodilators since the mid-1980s, principally involving the use of CCBs. It has been increasingly recognised that only a small number of patients with IPAH who demonstrate a favourable response to acute vasodilator testing at the time of right heart catheterisation (RHC) do well with CCBs [17, 20].

An acute vasodilator challenge performed during RHC can identify patients who may benefit from long-term treatment with CCBs [20]. In order to minimise the potential risks, acute vasodilator testing should only be performed with short-acting pulmonary vasodilators at the time of initial RHC and in experienced centres. Currently, nitric oxide (NO) is the agent most often used in acute testing [20]; based on previous experiences [17, 21, 22], *i.v.* epoprostenol and *i.v.* adenosine may also be used. A positive acute vasoreactive response (positive acute responder) is defined as a $\geqslant$10-mmHg reduction of mean pulmonary arterial pressure ($P_{pa}$) to reach an absolute value of $\leqslant$40 mmHg mean $P_{pa}$ with an increased or unchanged cardiac output [23, 24]. Generally, only about 10% of patients with IPAH will meet these criteria [21].

Favourable clinical and prognostic effects of high doses of CCBs in vasoreactive patients with IPAH have been shown in single-centre, non-randomised, non-controlled studies [17, 20]. However, it would appear unethical to withhold therapy with high-dose CCBs in a patient with a consistent reduction in $P_{pa}$ by acute pharmacological testing, and to perform a placebo-controlled clinical trial in these subjects [25]. Empirical treatment with CCBs without an acute vasoreactivity test is strongly discouraged due to possible severe adverse effects. The CCBs that have been predominantly used are nifedipine, diltiazem and amlodipine, with particular emphasis with the first two. The dosages of these drugs that have shown efficacy in IPAH are relatively high, *i.e.* up to

120–240 mg·day$^{-1}$ for nifedipine, 240–720 mg·day$^{-1}$ for diltiazem [17], and up to 20 mg of amlodipine. It is advisable to start with reduced doses (*i.e.* 30 mg of extended-release nifedipine *b.i.d.*, 60 mg of diltiazem *t.i.d.* or 5 mg of amlodipine *o.d.*) and then increase cautiously and progressively in the subsequent weeks to the maximal tolerated regimen. About 10% of patients with IPAH will meet the criteria for a positive acute vasoreactive response, and only half of these will also be clinical and haemodynamic long-term responders to treatment with CCBs. It is commonly accepted that continuation of CCBs is only warranted in these cases as a single treatment. Vasodilator responsiveness does not appear to predict a favourable long-term response to therapy with CCBs in patients with PAH and CTDs, and tolerance of high-dose CCBs is unusual in such patients.

## Endothelin receptor antagonists

Activation of the endothelin (ET) system has been demonstrated in both the plasma and lung tissue of PAH patients [26]. Although it is not clear whether the increases in ET-1 plasma levels are a cause or a consequence of PH [27], these data support a prominent role for the ET system in the pathogenesis of PAH [28]. ET-1 exerts vasoconstrictor and mitogenic effects by binding to two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, $ET_A$ and $ET_B$ receptors. $ET_B$ receptors are also present in endothelial cells, and their activation leads to the release of vasodilators and antiproliferative substances, such as NO and prostacyclin, which may counterbalance the deleterious effects of ET-1. Despite potential differences in receptor isoform activity, the efficacy in PAH of the dual $ET_A$ and $ET_B$ receptor antagonist drugs and the selective $ET_A$ receptor antagonist compounds appear to be comparable.

### *Bosentan*

Bosentan is an orally active dual $ET_A$ and $ET_B$ receptor antagonist and the first molecule of its class that was synthesised. Bosentan has been evaluated in PAH (IPAH, associated with CTD and Eisenmenger's syndrome) in five randomised controlled trials (Pilot, BREATHE (Bosentan Randomised trial of Endothelin Antagonist THErapy)-1, BREATHE-2, BREATHE-5 and EARLY (Endothelin Antagonist tRial in mildLY symptomatic pulmonary arterial hypertension patients)), which have shown improvement in exercise capacity, functional class, haemodynamics, echocardiographic and Doppler variables, and time to clinical worsening [29–33]. Two randomised controlled trials exclusively enrolled patients in WHO functional class II [32] or patients with Eisenmenger's syndrome [33]. This resulted in regulatory authority approval for the use of bosentan in the treatment of PAH patients in WHO functional class II and also in patients with PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. A study performed in PAH associated with sickle cell disease was prematurely terminated for slow enrolment [34]. Bosentan treatment commences at a dose of 62.5 mg *b.i.d.* and is uptitrated to 125 mg *b.i.d.* after 4 weeks. In paediatric patients, doses are reduced according to body weight and a paediatric formulation is available [35]. Long-term observational studies have demonstrated the durability of the effect of bosentan in adult IPAH patients over time [36]. Increases in hepatic aminotransferases occurred in approximately 10% of the subjects but were found to be dose-dependent and reversible after dose reduction or discontinuation. For these reasons, a liver function test should be performed monthly in patients receiving bosentan. Reductions in haemoglobin levels and impaired spermatogenesis have also been observed.

### *Sitaxentan*

Sitaxentan, a selective orally active $ET_A$ receptor antagonist, has been assessed in two randomised controlled trials (STRIDE (Sitaxentan To Relieve ImpaireD Exercise) 1 and 2) in patients in WHO functional class II and III [37, 38]. Aetiology included IPAH and PAH associated with CTDs or CHD. The studies demonstrated improvements in exercise capacity and haemodynamics. A 1-year, open-label observational study demonstrated the durability of the effects of sitaxentan over time [39]. Incidence of abnormal liver function tests appeared to be 3–5% for the approved dose of 100 mg *o.d.* Sitaxentan was initially authorised by the EMA as Thelin (Pfizer, New York, NY,

USA) in 2006. However, in December 2010, the manufacturer withdrew Thelin from the worldwide market following information on nine cases of severe hepatitis-like drug reactions (four deaths and one heart, lung and liver transplantation) [40]. Marketing authorisation was then also withdrawn by the EMA.

### *Ambrisentan*

Ambrisentan is a non-sulfonamide, propanoic acid-class ERA that is selective for the ETA receptor. Ambrisentan has been evaluated in a pilot study [41] and in two large randomised controlled trials (ARIES 1 and 2) [42], which have demonstrated efficacy on symptoms, exercise capacity, haemodynamics and time to clinical worsening of patients with IPAH and PAH associated with CTD and HIV infection. An open-label continuation study has demonstrated the durability of the effects of ambrisentan [42, 43]. Ambrisentan has been approved for the treatment of WHO functional class II and III patients. The current approved dose is 5 mg *o.d.*, which can be increased to 10 mg *o.d.* when the drug is tolerated at the initial dose.

The incidence of an abnormal liver function tests ranges 0.8–3%. In a small group of patients in which treatment with either bosentan or sitaxentan was discontinued due to liver function test abnormalities, ambrisentan at a dose of 5 mg was well tolerated [44]. Nevertheless, monthly assessment with a liver function test is recommended. In the USA, the document reporting the monthly liver test assessment is no longer required to obtain additional drug doses. An increased incidence of peripheral oedema has been reported with ambrisentan use.

## Phosphodiesterase type-5 inhibitors

Inhibition of the cyclic guanosine monophosphate (cGMP)-degrading enzyme PDE-5 results in vasodilatation through the NO/cGMP pathway at sites expressing this enzyme. Since the pulmonary vasculature contains substantial amounts of PDE-5, the potential clinical benefit of PDE-5 I has been investigated in PAH. In addition, PDE-5 I exert antiproliferative effects [45, 46]. All three PDE-5 I approved for the treatment of erectile dysfunction, sildenafil, tadalafil and vardenafil, cause significant pulmonary vasodilation with maximum effects observed after 60, 75–90 and 40–45 minutes, respectively [47].

### *Sildenafil*

Sildenafil is an orally active, potent and selective inhibitor of PDE-5. A number of uncontrolled studies have reported favourable effects of sildenafil in IPAH, PAH associated with CTD and CHD, and chronic thromboembolic pulmonary hypertension (CTEPH) [48–50]. A randomised controlled trial (SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) trial) performed in 278 PAH patients treated with sildenafil 20, 40 or 80 mg *t.i.d.* has confirmed favourable results on exercise capacity, symptoms and haemodynamics [51]. A *post hoc* analysis of 84 patients with PAH associated with CTD and who were receiving sildenafil in the SUPER-1 trial, revealed improvements in exercise capacity, haemodynamic parameters and functional class at 12 weeks when compared with placebo [52]. The approved dose is 20 mg *t.i.d.* but the durability of effect has been demonstrated with the dose of 80 mg *t.i.d.* [53]. A recently published randomised controlled trial has reported the favourable effects of sildenafil in 235 paediatric PAH patients [54].

The PACES (Pulmonary Arterial Hypertension combination Study of Epoprostenol and Sildenafil) trial [55], addressing the effects of adding sildenafil to epoprostenol, is discussed in the Combination therapy section of this chapter. Most side-effects of sildenafil were mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis).

### *Tadalafil*

Tadalafil is a once daily-dispensed, selective PDE-5 I, currently approved for the treatment of erectile dysfunction. A randomised controlled trial (PHIRST (Pulmonary Arterial Hypertension and

Response to Tadalafil) study group) on 406 PAH patients (about 50% of whom were on background bosentan therapy) treated with tadalafil 5, 10, 20 or 40 mg *o.d.* has shown favourable results on exercise capacity, symptoms, haemodynamics and time to clinical worsening at the largest dose [56]. The side-effect profile was similar to that of sildenafil.

### *Vardenafil*

Vardenafil is a PDE-5 I that was approved for the treatment of erectile dysfunction in 2005. A randomised controlled trial performed in 76 naïve PAH patients reported favourable results for vardenafil on exercise capacity, haemodynamics and clinical worsening [57].

## Prostanoids

Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilatation of all vascular beds. This compound is the most potent endogenous inhibitor of platelet aggregation and it also appears to have both cytoprotective and antiproliferative activities [58]. Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH, as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites [59]. The clinical use of prostacyclin in patients with PAH has been extended by the synthesis of stable analogues that possess different pharmacokinetic properties but share qualitatively similar pharmacodynamic effects.

### *Epoprostenol*

Epoprostenol (synthetic prostacyclin) is available as a stable, freeze-dried preparation that needs to be dissolved in alkaline buffer for *i.v.* infusion. Epoprostenol has a short half-life (3–5 minutes) and is stable at room temperature for only 8 hours. This explains why it needs to be administered continuously by means of an infusion pump and a permanent tunnelled catheter. The efficacy of continuous *i.v.* administration of epoprostenol has been tested in three unblinded randomised controlled trial in patients with IPAH [60, 61] and in those with PAH associated with the scleroderma spectrum of diseases [62]. Epoprostenol improves symptoms, exercise capacity and haemodynamics in both clinical conditions, and is the only treatment shown to improve survival in IPAH in a randomised study [61]. Long-term persistence of efficacy has also been shown in IPAH [63, 64], as well as in other APAH conditions [65–67] and in inoperable CTEPH [68].

Treatment with epoprostenol is initiated at a dose of 2–4 $ng \cdot kg^{-1} \cdot min^{-1}$, with doses increasing at a rate limited by side-effects (flushing, headache, diarrhoea, leg pain). The optimal dose varies between individual patients, ranging in the majority between 20 and 40 $ng \cdot kg^{-1} \cdot min^{-1}$ [63, 64].

Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. Guidelines for the prevention of central venous catheter blood stream infections have recently been proposed [69]. Abrupt interruption of the epoprostenol infusion should be avoided as, in some patients, this may lead to a rebound PH with symptomatic deterioration and even death.

### *Iloprost*

Iloprost is a chemically stable prostacyclin analogue available for *i.v.*, oral and aerosol administration. Inhaled therapy for PAH is an attractive concept that has the theoretical advantage of being selective for the pulmonary circulation. Inhaled iloprost has been evaluated in one randomised controlled trial (AIR (Aerosolized Iloprost Randomized) study group) in which daily repetitive iloprost inhalations (six to nine times, 2.5–5 μg per inhalation, median 30 μg daily) were compared with placebo inhalation in patients with PAH and CTEPH [70]. The study showed an increase in exercise capacity and improvement in symptoms, PVR and clinical events in enrolled patients. A second randomised controlled trial (STEP) performed in 60 patients who had already been treated with bosentan, showed an increase in exercise capacity ($p<0.051$) in the subjects randomised to the addition of inhaled iloprost in comparison with placebo [71]. Overall,

inhaled iloprost was well tolerated, with flushing and jaw pain being the most frequent side-effects. Continuous *i.v.* administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH [72]. The effects of oral iloprost have not been assessed in PAH.

### *Treprostinil*

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature. These characteristics allow *i.v.* administration of the compound as well as *via* the *s.c.* route. The *s.c.* administration of treprostinil can be accomplished by a micro-infusion pump and a small *s.c.* catheter.

The effects of treprostinil in PAH patients were studied in the largest worldwide randomised controlled trial performed in this condition, and showed improvements in exercise capacity, haemodynamics and symptoms [73]. The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate upper-quartile dosage levels ($>13.8$ ng·kg$^{-1}$·min$^{-1}$). Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in 8% of cases on active drug, and limiting dosage increase in an additional proportion of patients [73]. Among the 15% of patients who continued to receive *s.c.* treprostinil alone, survival appeared to improve [74]. In another long-term, open-label study, a sustained improvement in exercise capacity and symptoms with *s.c.* treprostinil was reported in patients with IPAH or CTEPH, with a mean follow-up of 26 months [75]. Treatment with *s.c.* treprostinil is initiated at a dose of 1–2 ng·kg$^{-1}$·min$^{-1}$, with doses increasing at a rate limited by side-effects (local site pain, flushing, headache). The optimal dose varies between individual patients, ranging in the majority between 20 and 80 ng·kg$^{-2}$·min$^{-1}$. Treprostinil has recently been approved in the USA for *i.v.* use in PAH patients who do not tolerate the *s.c.* formulation; the effects appear to be comparable with epoprostenol but at a dose that is two to three times higher [76, 77]. It is more convenient for the patient because the reservoir can be changed every 48 hours as compared to 12 hours with epoprostenol. A phase III randomised controlled trial (TRIUMPH (TReprostinil sodium Inhalation Used in the Management of Pulmonary arterial Hypertension)) of inhaled treprostinil in patients on background therapy with either the ERA bosentan or the PDE-5 I sildenafil has shown mild to moderate improvements in exercise capacity [78]. Durability of the effects has also been reported [78].

The efficacy of oral treprostinil has been tested in three randomised controlled trials in PAH patients (FREEDOM studies, not published). The two studies performed in patients on background therapy with ERA and/or PDE-5 I did not met the primary end-point of exercise capacity. The randomised controlled trial performed in naïve PAH patients has shown mild to moderate improvements on exercise capacity.

### *Beraprost*

Beraprost was the first chemically stable and orally active prostacyclin analogue. An randomised controlled trial performed by the ALPHABET (Arterial Pulmonary Hypertension and Beraprost European) study group [79] in Europe and a second study in the USA [80] used this compound and showed an improvement in exercise capacity that unfortunately only persisted for up to 3–6 months. There were no haemodynamic benefits. The most frequent adverse events were headache, flushing, jaw pain and diarrhoea.

## New candidate compounds

In this section, we will discuss the information that is available about future candidate compounds in phase III drug development. Currently, none of the reported compounds has been approved for the treatment of PAH patients.

### Macitentan

Macitentan is a novel dual ERA that possesses sustained receptor-binding and tissue-penetration properties. The preliminary results of a pivotal randomised controlled trial performed in 742 PAH patients (SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome)) has been recently reported in a press release [81]. Macitentan, at both the 3- and 10-mg dose, decreased the risk of a morbidity/mortality event over the treatment period *versus* placebo, and was well tolerated. More information is expected in the next few months, together with submission for regulatory approval.

### Selexipag

Selexipag is an orally available, selective prostacyclin receptor (IP receptor) agonist. A randomised controlled trial in 43 PAH patients showed a 30% reduction of PVR and a non-statistically significant increase of exercise capacity as compared with placebo after 17 weeks of treatment (including a dose up-titration period) [82]. A large phase III morbidity/mortality randomised controlled trial study is currently ongoing.

### Riociguat

Riociguat stimulates soluble guanylate cyclase (sGC) independently of NO and increases the sensitivity of sGC to NO, resulting in increased cGMP. Drugs that increase cGMP levels, such as PDE-5 I, promote pulmonary vasorelaxation and possess antiproliferative effects. An uncontrolled multicentre study showed that riociguat is able to improve haemodynamics and exercise capacity in PAH and CTEPH patients [83]. Two randomised controlled trials are currently testing the ability of riociguat to increase exercise capacity in patients with PAH (PATENT (Pulmonary Arterial Hypertension sGC-Stimulator Trial)) and CTEPH.

### Imatinib

Imatinib is an antiproliferative agent developed to target the BCR-abl tyrosine kinase in patients with chronic myeloid leukaemia. In addition, the inhibitory effects of imatinib on platelet-derived growth factor receptors $\alpha$ and $\beta$ and c-KIT suggest that it may be efficacious in PAH. A phase II randomised controlled trial study performed in 59 patients reported that imatinib significantly improved pulmonary haemodynamics [84]. In a phase III study (IMPRES), which was performed in PAH patients on background therapy with at least two approved drugs, improvements in exercise capacity and haemodynamics were demonstrated in comparison with placebo (unpublished data). However, serious adverse events and discontinuations were more frequent with imatinib than placebo, and additional data are required to clarify the benefit to risk ratio of this compound in the treatment of PAH patients.

## Combination therapy

The term ''combination therapy'' describes the simultaneous use of more than one PAH-targeted class of drugs, *e.g.* ERAs, PDE-5 I, prostanoids and novel substances. Combination therapy has become the standard of care in many PAH centres, although long-term safety and efficacy have not yet been amply explored. Numerous case series have suggested that various drug combinations appear to be safe and effective [85–88]. In one series, a step-wise use of combination therapy according to predefined treatment goals was associated with an improved outcome compared with a historical control group [89].

Results of randomised controlled trials that have evaluated combination therapy for PAH have been published. The STEP-1 study addressed the safety and efficacy of 12 weeks of therapy with inhaled iloprost and bosentan, and found a marginal increase in the post-inhalation 6-minute

walking distance (6MWD) +26 m ($p=0.051$) [71]. When measured at pre-inhalation, the placebo-corrected improvement in 6MWD was +19 m ($p=0.14$). There was no improvement in pre-inhalation haemodynamics in the iloprost group after 12 weeks of treatment, but time to clinical worsening was significantly prolonged in the iloprost group (no events *versus* five events in the placebo group; $p=0.02$). In contrast, another randomised controlled trial (COMBI (COMbination therapy of Bosentan and aerosolised Iloprost in idiopathic pulmonary arterial hypertension)), which also studied the effects of inhaled iloprost added to bosentan, was stopped prematurely after a planned futility analysis did not show an effect on 6MWD or time to clinical worsening [90].

Two other randomised controlled trials on combination therapy have been concluded: TRIUMPH [78] and PACES [55]. TRIUMPH studied the effects of inhaled treprostinil in patients already treated with bosentan or sildenafil. The primary end-point, change in 6MWD at peak exposure, improved by 20 m compared with placebo ($p<0.0006$). At trough exposure, *i.e.* more than 4 hours post-inhalation, the difference was 14 m in favour of the treprostinil group ($p<0.01$). There were no significant differences in Borg dyspnoea index, functional class and time to clinical worsening [78].

The PACES trial addressed the effects of adding sildenafil to epoprostenol in 267 PAH patients. The most pertinent findings of the study were significant improvements in 6MWD and time to clinical worsening after 12 weeks. It is worth noting that seven deaths occurred in this trial, all in the placebo group [55].

In the subgroup of patients enrolled in the EARLY study (bosentan in WHO functional class II PAH patients) who were already on treatment with sildenafil, the haemodynamic effect of the addition of bosentan was comparable to that achieved in patients without background sildenafil treatment [32]. A pharmacokinetic interaction has been described between bosentan and sildenafil, which act as inducers or inhibitors of cytochrome (CY)P450 3A4, respectively. The co-administration of both substances results in a decline of sildenafil plasma levels and an increase in bosentan plasma levels [91]. So far, there is no indication that these interactions are associated with reduced safety [92] but the issue as to whether the clinical efficacy of sildenafil is significantly reduced is still under debate. No pharmacokinetic interactions have been reported between sildenafil and ambrisentan.

In the subgroup of PAH patients on background bosentan therapy enrolled in the PHIRST study, the addition of tadalafil increased exercise capacity even if the difference was not statistically significant [56, 93].

The most recent treatment algorithm from the ESC/ERS guidelines for PAH recommends a sequential approach to combination therapy [1]. According to the guidelines, patients should be started on monotherapy and followed-up regularly. If an inadequate clinical response is observed on monotherapy, the addition of further therapy can be considered. Starting patients on combination therapy, known as ''initial combination therapy'', is another potential approach. Despite the possibility that such aggressive treatment of PAH could prevent clinical deterioration, it should only be considered for treatment of the most severely affected patients in WHO functional class IV, as little supporting evidence exists [31, 94].

## Treatment algorithm

The treatment algorithm for PAH patients, reported in the ESC/ERS PH guidelines [1, 95] published in 2009, can still be considered up to date (fig. 1).

The treatment algorithm does not apply to patients in other clinical groups, particularly patients with PH associated with left heart disease or with lung diseases. In addition, the different treatments have been evaluated by randomised controlled trials mainly performed in IPAH, heritable PAH, PAH due to anorexigen drugs and PAH associated with CTD or with CHD (either surgically corrected or not surgically corrected). The grades of recommendation and levels of evidence for the other PAH subgroups are lower.

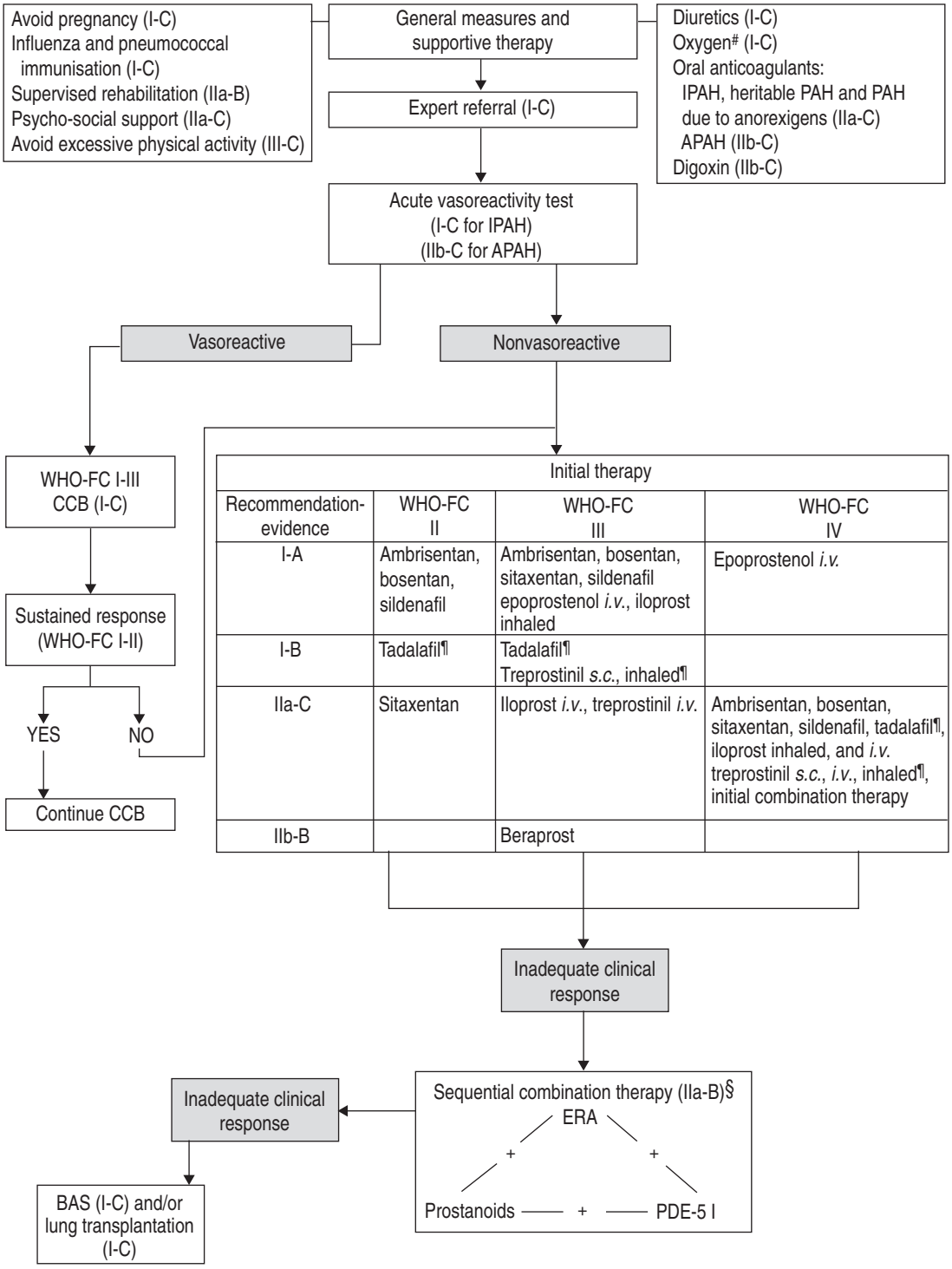


**Figure 1.** Treatment algorithm from the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines on pulmonary hypertension [1]. Sitaxentan has since been withdrawn for hepatotoxicity. APAH: associated pulmonary arterial hypertension (PAH); BAS: balloon atrial septostomy; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; IPAH: idiopathic PAH; PDE-5 I: phosphodiesterase type-5 inhibitor; WHO-FC: World Health Organization functional class. #: to maintain arterial blood oxygen pressure >8 kPa (60 mmHg); ¶: under regulatory review in the European Union; §: IIa-C for WHO-FC II. Reproduced from [1] with permission from the publisher.

The suggested initial approach after the diagnosis of PAH is the adoption of the general measures, the initiation of supportive therapy and referral to an expert centre.

Acute vasoreactivity testing should be performed in all patients with PAH, although patients with IPAH, heritable PAH and PAH associated with anorexigen use are the most likely to exhibit an acute positive response and to benefit from therapy with high-dose CCBs. Vasoreactive patients, as defined above, should be treated with optimally tolerated doses of CCBs; an adequate response should be confirmed after 3–4 months of treatment.

Non-responders to acute vasoreactivity testing who are in WHO functional class II should be treated with an ERA or a PDE-5 I. Non-responders to acute vasoreactivity testing or responders who remain in (or progress to) WHO functional class III should be considered candidates for treatment with either an ERA, a PDE-5 I or a prostanoid.

As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. In this case, the choice of the drug is dependent on a variety of factors, including approval status, route of administration, side-effect profile, patients' preferences and physicians' experience. Some experts still use first-line *i.v.* epoprostenol in WHO functional class III patients because of its survival benefits.

Continuous *i.v.* epoprostenol is recommended as first-line therapy for WHO functional class IV PAH patients because of the survival benefit in this subset. Treprostinil administered *s.c.* and *i.v.* has also been approved for the treatment of WHO functional class IV patients in the USA. Although no randomised controlled trials have been performed for the *i.v.* delivery of iloprost, this prostacyclin analogue has been approved in New Zealand.

Although ambrisentan, bosentan and sildenafil are approved in WHO functional class IV patients in the USA, only a small number of these patients were included in the randonised controlled trials of these agents. Accordingly, most experts consider these treatments as a second line in severely ill patients.

In WHO functional class IV patients, initial combination therapy may also be considered.

In case of inadequate clinical response, sequential combination therapy should be considered. Combination therapy can either include an ERA plus a PDE-5 I, a prostanoid plus an ERA, or a prostanoid plus a PDE-5 I. Appropriate protocols for timing and dosing to limit possible side-effects of the combination still have to be defined.

Balloon atrial septostomy and/or lung transplantation are indicated for PAH with inadequate clinical response, despite optimal medical therapy, or where medical treatments are unavailable. These procedures should only be performed in experienced centres.

### *Statement of Interest*

N. Galiè has been involved with the steering committee activities for Eli Lilly and Company, Actelion, Pfizer, Bayer-Schering, GlaxoSmithKline and Novartis. He has also been a paid lecturer for Actelion, Pfizer, Bayer-Schering, Eli Lilly and Company and GlaxoSmithKline. N. Galiè has performed contract research for Actelion, Pfizer, United Therapeutics, Bayer-Schering, GlaxoSmithKline and Novartis. A. Manes has received fees for speaking from Actelion Pharmaceuticals, Pfizer, Lilly and GlaxoSmithKline. M. Palazzini has received fees for speaking from Actelion Pharmaceuticals, Pfizer, Bayer, Lilly and GlaxoSmithKline.

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# Chapter 4

# Pulmonary arterial hypertension in connective tissue diseases

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**SUMMARY: Pulmonary arterial hypertension (PAH) is a common complication of connective tissue diseases (CTD) and a leading cause of death in this population. Despite significant advances in therapy for PAH, particularly for idiopathic PAH (IPAH), the response to treatment in patients with CTD associated with PAH, mainly in scleroderma-associated PAH (SSc-PAH), has been quite disappointing. This chapter reviews the epidemiology, clinical manifestations, pathophysiology and currently available therapies for CTD-associated PAH with a particular focus on SSc-PAH, animal models of disease, and newly identified potential targets for therapy for this devastating syndrome.**

**KEYWORDS: Connective tissue disease, pulmonary arterial hypertension, systemic sclerosis, therapy**

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Pulmonary arterial hypertension (PAH) is a relentlessly progressive disease, consisting of structural remodelling and obliteration of the pulmonary distal vessels, with significant morbidity leading eventually to death through right ventricular (RV) failure [1, 2]. PAH, or Group 1 of the classification of pulmonary hypertension (PH), includes several clinical entities sharing similar pathological alterations, among them idiopathic PAH (IPAH) and heritable PAH (associated with known or presumed gene defects), and PAH associated with diseases or conditions such as connective tissue diseases (CTD), porto-pulmonary hypertension, infectious conditions (*e.g.* HIV) and drugs and toxins [3].

While the histological changes of PAH have been well characterised [4], the cellular and molecular mechanisms underlying this syndrome remain poorly understood [5]. However, there has been a growing interest in autoimmunity and inflammatory processes as putative driving forces in the development of pulmonary vascular changes [6] based on several clinical observations, including the presence of circulating autoantibodies [7] and pro-inflammatory cytokines (*e.g.* interleukin (IL)-1 and IL-6) [8], in patients with IPAH and the common association of PAH with autoimmune diseases such as systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). In this chapter, we will review the characteristics of PAH associated with CTD, with special emphasis

on SSc-PAH since it is the most common but also most severe syndrome among all forms of CTD including SLE, mixed connective tissue disease (MCTD), rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome.

## Pathology of vascular remodelling in SSc-PAH

Two recent studies [9, 10] support the hypothesis of SSc-PAH as a distinct clinical entity and outline histopathological differences of vascular remodelling in IPAH compared with SSc-PAH. Briefly, the main characteristic features of SSc-PAH compared with IPAH are: 1) a higher degree of intimal fibrosis, especially of small vessels; 2) the absence of plexiform lesions; 3) a more pronounced perivascular and interstitial inflammation/fibrosis; and 4) in particular the presence of pulmonary veno-occlusive disease (PVOD)-like changes. Although preliminary, these findings are intriguing and would need to be confirmed in larger studies, preferably with samples that do not only reflect late-stage disease.

One of the most interesting observations of these studies was the high proportion of PVOD in patients with SSc-PAH. PVOD is a rare subtype of PAH [11] with a prevalence of 0.1–0.2 per million persons and per year [12]. It is characterised by extensive and diffuse occlusion of pulmonary veins and venules. Capillary angiectasia and capillary angioproliferation with concomitant postcapillary congestion [11] represent additional features. The estimated proportion of PVOD in PAH is about 5–10% [13]. Interestingly, in the study by DORFMÜLLER *et al.* [9], 85% of patients with CTD-PAH (50% of which had SSc) showed PVOD-like features compared with 17.2% of patients with IPAH. In the study by OVERBEEK *et al.* [10], PVOD occurred in 50% of the patients with SSc-PAH whereas it was absent in patients with IPAH.

These histological characteristics, as well as other differences detailed below, may partly explain the fact that the two diseases have quite divergent clinical courses and response to therapy. Indeed, survival is significantly worse in SSc-PAH compared with IPAH patients treated with modern medical therapy [14–18].

### Inflammation and fibrosis

Current concepts of the development of vasculopathy in both IPAH and SSc-PAH support the role of pro-inflammatory cytokines such as IL-1 or IL-6 [8, 19–21], chemokines such as CX3CL1, CC chemokine (C-C motif) ligand 5 (CCL5), monocyte chemotactic protein (MCP)-1 [6] and growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) [6, 9, 10, 22]. Besides inflammatory processes, the presence of both intimal fibrosis and interstitial lung disease (ILD) might also account for the worse clinical performance and the observed differences in the diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) of patients with SSc-PAH compared with patients with IPAH [15, 23].

### Autoimmunity

Dysregulation of B-cells might play a role in the pathogenesis of SSc linking autoimmunity and fibrosis [19]. In SSc, levels of circulating CD19+ can be observed, whereas memory B-cells, although reduced in numbers, show markers of activation. In the skin and lungs of SSc patients, increased numbers of infiltrating B-cells and a dermal B-cell gene expression signature were reported [24]. Experimental mouse models of skin and lung fibrosis support a role of B-cells in autoimmunity and fibrosis [25]. Whether autoimmunity plays a preponderant role in (pulmonary) vasculopathy has yet to be addressed.

Autoantibodies are often associated with certain phenotypes in SSc and, thus, anti-fibrillarin [26, 27], anti-U1RNP [28], and anti-centromere antibodies [29] are commonly found in patients with SSc-PAH. So far, no functional properties have been found for these autoantibodies. However, there is increasing data on novel, potentially pathogenic autoantibodies in patients with IPAH and SSc-PAH.

Injury and apoptosis of endothelial cells are considered initial events in the pathogenesis of SSc [30, 31]. Anti-endothelial cell antibodies are found in patients with IPAH and SSc-PAH [32] and are suggested to play a role in the pathogenesis of PAH by displaying distinct reactivity against micro- and macrovascular antigens [33] and inducing the activation of EC and the expression of adhesion molecules leading finally to apoptosis [34, 35]. Recently, anti-β(2)-glycoprotein I antibodies were reported to be associated with PAH in SSc, although it has yet to be investigated whether these autoantibodies are pathogenic or simply represent a marker of endothelial cell injury [26, 36].

Key cellular players of vascular remodelling include vascular smooth muscle cells (VSMC) and activated fibroblasts. Immunoglobulin (Ig)G antibodies targeting stress-induced phosphoprotein 1 and α-enolase on the surface of VSMC have been identified in the serum of patients with SSc with/without PAH and IPAH and have been suggested to modulate vascular contraction, thus potentially contributing to the vascular remodelling [37]. Anti-fibroblast antibodies are present in the sera of patients with IPAH and SSc-PAH [38] and have been shown to induce pro-adhesive and pro-inflammatory responses in normal fibroblasts *in vitro* [39]. Furthermore, identified target antigens include proteins involved in cytoskeletal function, cell contraction and other key cellular pathways [40]. Therefore, it is possible that these anti-fibroblast antibodies might mediate the secretion of cytokines and growth factors involved in the vascular remodelling in PAH.

Recently, functional autoantibodies against vascular receptors were identified in the sera of patients with SSc [41, 42]. Antibodies against angiotensin II type 1 receptor and endothelin (ET)-1 type A receptor on endothelial cells were associated with more severe disease including complications such as PH, lung fibrosis and digital ulcers. Of note, both antibodies exerted biological effects by inducing the phosphorylation of extracellular signal-related kinase 1 or 2 and by increasing the expression of transforming growth factor (TGF)-β in endothelial cells which could be blocked by specific receptor antagonists [41].

Additionally, stimulatory antibodies targeting the PDGF receptor in SSc patients have been detected [43]. Given the key role of PDGF in the pathogenesis of IPAH and SSc-PAH, addressing the pathogenic role of these antibodies in the pulmonary vascular remodelling in SSc will be important.

## Epidemiology and clinical features of CTD-PAH

### SSc-PAH

SSc is a complex multi-system disorder characterised essentially by endothelial dysfunction, fibroblast dysregulation resulting in excess production of collagen, and profound alterations of the immune system [44]. In combination, such alterations lead to progressive fibrosis of the skin and internal organs resulting in premature organ failure and death. Genetic and environmental factors may contribute to host susceptibility [45, 46], however, the aetiology of the disease remains largely elusive. Whether in its limited or diffuse form, SSc has the potential for multiple organ involvement; foremost among them are the gastro-intestinal tract, heart, kidneys and lungs [44]. However, SSc-PAH has now emerged as one of the two leading causes of mortality [47, 48]. In this context, it is quite vexing that despite remarkable advances in disease-targeted therapies for other forms of PAH (such as IPAH), response to therapy remains largely suboptimal and survival rather dismal in SSc-PAH [14–17, 49].

#### *Prevalence and incidence*

Using strict right heart catheterisation (RHC) for diagnosis of PAH, the prevalence of SSc-PAH in prospective studies is between 7.8 and 12% [50–52], with variations probably dependent on referral biases. Given significant geographic variations in the prevalence of SSc, and with an estimated US prevalence of SSc of about 240 cases per million, the overall prevalence of SSc-PAH (in the USA) may be as high as 24 individuals per million, a figure significantly higher than that of

the estimated prevalence of IPAH [12]. However, in two large registries of PAH, CTD-PAH (mainly represented by SSc) accounts for only 15.3% [12] and 25% (including 17% of SSc-PAH patients in the USA registry) of all PAH cases, suggesting a clear under recognition of the syndrome [53]. In a large single US centre registry, the proportion of SSc-PAH is about 30% of all PAH patients [54]. The overall higher prevalence of SSc in the USA [55] probably accounts for a somewhat higher prevalence of SSc-PAH in the USA compared with France. A recent prospective study estimates the incidence of PAH among patients with SSc at 0.61 cases per 100 patient-years [49].

### *Risk factors for the development of PAH in SSc*

An increased risk of developing PAH in the setting of SSc disease includes limited (as opposed to diffuse) skin involvement [23, 56, 57]; SSc disease duration greater than 10 years [57], although PAH can develop at any time throughout the course of SSc [49]; older age at the onset of SSc [52, 56]; and severity [23] or length of duration [58] of Raynaud phenomenon. Other clinical parameters, such as reduced nailfold capillary density [57, 59] or an isolated reduction in $D_{L,CO}$ or a progressive decline of $D_{L,CO}$ [23, 56], also appear to be independent risk factors for the subsequent development of PAH in these patients. While the decrease in $D_{L,CO}$ is probably the result of progressive pulmonary vascular remodelling over time, it is interesting to note that this alteration is significantly more pronounced in SSc-PAH compared with IPAH patients [15], perhaps suggesting more profound small vessel remodelling in the former compared with the latter patients, although this may also represent associated subclinical lung fibrosis in these patients.

### *Clinical features*

SSc-PAH patients are typically predominantly females (reflecting the sex predilection for SSc) with limited sclerosis; they are older and have a more favourable baseline haemodynamic profile compared with IPAH patients, although this is clearly misleading since their survival is worse [15, 16]. As in IPAH, presenting clinical symptoms are nonspecific and include mainly dyspnoea and functional limitation, the latter often being worse than in IPAH due to older age and frequent involvement of the musculoskeletal system. SSc-PAH patients also tend to have other organ involvement such as renal dysfunction and intrinsic heart disease. Even in the absence of PAH, SSc patients tend to have depressed RV function [60, 61] and left ventricular (LV) systolic as well as diastolic dysfunction [62]. At presentation, SSc-PAH patients have severe RV dysfunction similar to IPAH patients; however, they display more severely depressed RV contractility [63]. In addition, they are more likely to have LV diastolic dysfunction and evidence of pericardial effusion (34% compared with 13% for IPAH) [15]. The latter portends a particularly poor prognosis [15]. In addition, SSc-PAH patients often present with more severe metabolic abnormalities such as high levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) [64, 65] and hyponatraemia [66]. Both NT-proBNP and hyponatraemia, at baseline (or with serial changes (for NT-proBNP [64])) correlate with survival in PAH [64, 66].

### *Early diagnosis*

Because of a relatively high prevalence of PAH in SSc, there is an opportunity for early diagnosis in this population at risk, which can lead to therapeutic intervention at an earlier stage and potentially improved outcome. An algorithm for early detection of PAH based on a combination of symptoms and screening echocardiography was recently tested in a large French study encompassing a total of 21 referral centres. SSc patients with tricuspid regurgitation velocity (TRV) jet by transthoracic echocardiography greater than 3 $m \cdot s^{-1}$, or TRV between 2.5 and 3 $m \cdot s^{-1}$ if patients had unexplained dyspnoea, were systematically referred for RHC. Using this approach, incident cases of SSc-PAH with less haemodynamic impairment (compared with the ''prevalent'' patients, *i.e.* patients with known disease) were identified [51]. Whether this approach leads to improved outcomes [67, 68] or merely reflects a so-called ''lead bias'' remains to be determined in larger prospective studies. At any rate, it seems reasonable to recommend a routine diagnostic workup in those SSc patients with unexplained dyspnoea in the setting of low or declining single-breath $D_{L,CO}$ measurements,

echocardiographic findings suggestive of pulmonary hypertension (elevated TRV jet or dilated RV or atrium) and/or elevated levels of NT-proBNP [51].

### *Prognosis of SSc-PAH*

SSc-PAH patients are almost four times more likely to die from their disease than IPAH patients [15], and their outcome in general is significantly worse compared with patients with any other CTD complicated by PAH [14, 17]. Despite substantial improvements in other PAH categories, the figures remain sobering for these patients with a 3-year survival well below 60% [14, 15, 17, 49, 50, 69]. Markers of poor survival include male sex [17], late age at diagnosis [17], pericardial effusion [15], functional severity based on New York Heart Association (NYHA) functional class [17, 70], right heart dysfunction [15, 50, 70], hyponatraemia [66] and renal impairment [70]. In addition, measures of RV afterload, both proximal and distal vascular resistance (pulmonary arterial capacitance estimated by stroke volume divided by pulmonary artery pulse pressure and pulmonary vascular resistance (PVR), respectively) independently predict survival in SSc-PAH [70]. Finally, in patients with SSc-PAH admitted to the hospital for treatment of RV failure, hyponatraemia and hypotension upon admission are the main prognostic factors for in-hospital mortality. Furthermore, short-term outcomes after discharge are poor and remarkably worse in patients with underlying CTD, with mortality close to 50% within the following year after discharge [71].

## Systemic lupus erythematosus

Similar to SSc, endothelial dysfunction in SLE may be prominent in this disease, resulting in a potential imbalance between vasodilators and vasoconstrictors. Other causes of pulmonary vascular disease and PH in SLE include recurrent thromboembolic disease, particularly in patients with anti-phospholipid antibodies (such as anti-cardiolipin antibody present in up to 10% of patients with SLE) [72], pulmonary vasculitis and parenchymal disease (including ILD and the shrinking lung syndrome from myositis of the diaphragm). Combined vasculitis and chronic hypoxia are frequent contributing offenders in these syndromes. In addition, pulmonary venous hypertension can be a consequence of LV dysfunction and myocarditis.

The exact prevalence of PAH in SLE remains unclear but is in the order of about 0.5–14% patients (most certainly less than in SSc) based on a review of the literature encompassing over 100 patients [73]. The patients are predominantly female (90%), young (average age of 33 years at the time of diagnosis), and often suffer from Raynaud's phenomenon (underscoring a generalised endothelial dysfunction in these patients with SLE and PH). The pathological lesions are often indistinguishable from IPAH or SSc-PAH lesions, with intimal hyperplasia, smooth muscle cell hypertrophy and medial thickening. Survival, initially thought to be quite poor (25–50% at 2 years) in studies preceding specific PAH treatment, is now estimated at 75% at 3 years [17], clearly significantly better than SSc-PAH.

## Mixed connective tissue disease

MCTD is a separate entity among the CTDs linked to anti-U1RNP antibodies. The main clinical features are Raynauds phenomenon, myositis/myopathy, polyarthritis and puffy fingers. The exact prevalence of PAH in MCTD is unknown and has been reported to be as high as 50% [74]. The syndrome may occasionally respond to immunosuppressive drugs [75, 76] and, therefore, these patients appear to have a better prognosis overall compared with SSc-PAH patients with an estimated 2- and 3-year survival of 89 and 63%, respectively [17].

## Rheumatoid arthritis

PAH is a rare complication of rheumatoid arthritis and both the prevalence and impact of PH in these patients is not well known. The 2- and 3-year estimated survival in these patients is 83 and 66%, respectively [17].

### Primary Sjögren's syndrome

Although primary Sjögren's syndrome is a relatively common autoimmune disease with glandular and extraglandular manifestations, it is very rarely complicated by PAH. In a recent review by LAUNAY *et al.* [77] of 28 well characterised patients with primary Sjögren's syndrome and PAH, the mean age at diagnosis of PAH of these almost exclusively female patients (27 out of 28 patients) was 50 years. Patients had severe functional class (III and IV) and haemodynamic impairment. Standard therapy (with endothelin receptor antagonists (ERAs), phosphodiesterase inhibitors or prostanoids) was typically ineffective despite an initial improvement. Some patients were reported to respond to immunosuppressive treatment. However, conclusion regarding treatment is limited by the small size of this case report. Survival rate was low (66% at 3 years) [77].

## Therapies for CTD-PAH

### General measures

General guidelines for the treatment of PAH include the use of supplemental oxygen in patients who are hypoxic at rest or with exercise and in patients who have evidence of oxygen desaturation at night. Loop diuretics are used in most patients at variable dosages for the management of volume overload and in acute situations of right heart failure. Digitalis may be used as adjunct therapy for the management of symptomatic right heart failure and sometimes for control of atrioventricular conduction [78].

### Calcium channel blockers

Treatment for PAH over the past 20 years has largely resulted from the recognition of a profoundly impaired pulmonary vascular endothelial function [79–81] with consequent alterations in both vascular tone and remodelling [82]. Early on, vasodilator therapy with high dose calcium channel blockers (CCB) was found to be an effective long-term therapy [83], but only for a minority of patients (~6% of IPAH patients [84]) who demonstrated acute vasodilation upon challenge (*e.g.* to nitric oxide (NO) or adenosine) during cardiac haemodynamic testing. However, high dose calcium channel therapy is not indicated for patients with CTD-PAH such as SSc-PAH since there are only about 2.6% responders in that group in one large study [12], and long-term response to these drugs remains very rare in these patients [85]. CCB remain the norm for treatment of Raynaud phenomenon.

### Anti-inflammatory drugs

It is now increasingly recognised that inflammation may play a significant role in various types of PH, including IPAH and CTD-PAH. However, only rare patients with CTD-PAH (mainly patients with SLE, primary Sjögren syndrome, and MCTD) have had anecdotal dramatic improvement of their pulmonary vascular disease with corticosteroids and/or conventional immunosuppressive therapy [75, 76]. However, clearly SSc-PAH patients have been recalcitrant to such therapy [75].

### Prostaglandin analogues

Prostacyclin (epoprostenol), which has potent pulmonary vasodilator activity but also anti-platelet aggregating and antiproliferative properties [86], given by continuous infusion has proven effective in improving the exercise capacity, cardiopulmonary haemodynamics, NYHA functional class, symptoms and survival in IPAH patients [87–89]. In SSc-PAH, continuous intravenous epoprostenol marginally improves exercise capacity and haemodynamics [90], compared with conventional therapy, and may have long-term beneficial effects [91]; however, an effect on survival in these patients has yet to be demonstrated.

Treprostinil, an analogue of epoprostenol suitable for continuous subcutaneous administration, has modest effects on symptoms and haemodynamics in PAH [92]. In a small study of 16 patients (including six CTD-PAH patients), *i.v.* treprostinil improved haemodynamics, 6-minute walking distance (6MWD) and functional class [93]. Although the safety profile of this drug is similar to *i.v.* epoprostenol, required maintenance doses are usually twice as much as for epoprostenol. However, for patients with SSc-PAH, the lack of requirement of ice packing and less frequent mixing of the drug offer obvious advantages.

The use of prostacyclin analogues in SSc-PAH patients has been limited by occasional reports of pulmonary oedema, raising the suspicion of increased prevalence of PVOD in these patients [94, 95]. However, this remains a therapeutic option for patients with SSc-PAH with NYHA class IV with the caveat that frequent digital problems and disabilities that these patients often experience, and the number of serious adverse effects associated with this form of therapy (*e.g.*, infection and possibility of pump failure [96]), may render treatment quite challenging.

## Endothelin receptor antagonists

Randomised, placebo-controlled trials have now established the beneficial effect of bosentan therapy on functional class, 6MWD, time to clinical worsening and haemodynamics in PAH [97, 98]. In these trials, roughly one-fifth of the population consisted of SSc-PAH patients while a large majority had a diagnosis of IPAH. In subgroup analysis, a nonsignificant trend towards a positive treatment effect on 6MWD was shown for SSc-PAH patients treated with bosentan compared with placebo [98]. At most, bosentan therapy prevented deterioration in these patients (as assessed by a stable 6MWD in the treated group compared with a substantial decrease in the placebo group). However, in another analysis of patients with CTD-PAH (*e.g.* SLE, overlap syndrome and other rheumatological disorders) included in several randomised clinical trials of bosentan, there was a trend toward improvement in 6MWD and improved survival compared with historical cohorts [99]. Single-centre experience suggests that long-term outcome of first-line bosentan monotherapy is inferior in SSc-PAH compared with IPAH patients, with no change in functional class and worse survival in the former group [69]. Considering that ET-1 may be an important player in the development of vascular lesions in SSc-PAH, perhaps contributing to vascular damage and fibrosis, inhibiting ET-1 remains a rational strategy. In a small study of SSc patients (10 of whom had SSc-PAH), bosentan treatment appeared to reduce endothelial cells (as determined by endothelial soluble serum factors such as intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, P-selectin and platelet/endothelial cell adhesion molecule (PECAM)-1) and T-cell subset (assessed by expression of lymphocyte function-associated antigen-1, very late antigen-4, and L-selectin on CD3 T-cells) activation [100]. An additional beneficial effect of bosentan therapy is a significant reduction in the occurrence of new digital ulcerations without, however, evidence of healing of pre-existing ulcers [101].

The selective ETA receptor antagonist sitaxentan improved exercise capacity (*i.e.* change in peak oxygen uptake ($V'O_2$) at week 12, the main end-point of the study) [102] and, in patients with CTD-PAH (representing less than one-quarter of the study group), improved exercise capacity, quality of life and haemodynamics, although elevated liver enzymes were reported [103]. This drug has since been removed from the market due to significant hepatotoxicity and death in a few patients. A large placebo-controlled, randomised trial of ambrisentan, the only currently Food and Drug Administration (FDA)-approved selective ERA, improved 6MWD in PAH patients at week 12 of treatment, however, the effect was clearly larger in IPAH compared with CTD-PAH patients (range of 50–60 m *versus* 15–23 m, respectively) [104]. Ambrisentan is generally well tolerated although peripheral oedema (in up to 20% of patients [104]) and fluid overload are quite common side-effects often requiring an increase in diuretic dosage.

## Phosphodiesterase inhibitors

Sildenafil, a phosphodiesterase type-5 inhibitor (PDE-5 I) that reduces the catabolism of cyclic guanosine monophosphate (cGMP), thereby enhancing the cellular effects mediated by NO, has become a widely used and highly efficacious therapy for PAH. A large clinical trial showed that sildenafil therapy led to an improvement in the 6MWD in patients with IPAH and associated PAH (mainly CTD-PAH or repaired congenital heart disease (CHD)), who were predominantly functional class II or III, at all three doses tested (20, 40, and 80 mg, given three times daily) [105]. Based on the lack of significant differences in clinical effects and time to clinical worsening at week 12 between doses, the recommended dosage is now 20 mg three times daily. In a *post hoc* subgroup analysis of 84 patients with CTD-PAH (45% of whom had SSc-PAH), data from the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study suggest that sildenafil at a dose of 20 mg improved exercise capacity (6MWD), haemodynamic measures and functional class after 12 weeks of therapy [106]. However, for reasons that remain unclear (but in part related to study limitations such as *post hoc* subgroup analysis), there was no significant effect for 80 mg three times daily on haemodynamics in this CTD-PAH subgroup of patients [106]. For this reason and because of the potential of increased side-effects (such as bleeding from arterio-venous malformations) at high doses, a sildenafil dosage of 20 mg three times daily is recommended for SSc-PAH patients (and perhaps for patients with other forms of CTD-PAH) as standard initial therapy. Higher doses may occasionally be attempted in case of limited response. The impact of long-term sildenafil therapy on survival in these patients remains to be determined. Finally, tadalafil, another phosphodiesterase inhibitor, is also effective for PAH [107], although subgroup analysis has not been performed yet and thus its effects on CTD-PAH remain unclear. Tadalafil has the advantage over sildenafil of a single daily dosage.

## Combination therapy

Adding PAH drugs when patients fail to improve on monotherapy has now become routine. Adding inhaled iloprost to patients receiving bosentan has been shown to be beneficial in a small, randomised trial. Combining inhaled iloprost with sildenafil is mechanistically appealing and anecdotally efficacious [108, 109] as these drugs target separate, potentially synergistic pathways. Several multicentre trials are now exploring the efficacy of various combinations of oral drugs and inhaled drugs. The results of the Pulmonary Arterial Hypertension Combination study of Epoprostenol and Sildenafil (PACES) trial demonstrated that adding sildenafil (80 mg three times daily) to *i.v.* epoprostenol improves exercise capacity, haemodynamic measurements, time to clinical worsening and quality of life [110]. About 21% of these patients had CTD-PAH, including 11% with SSc-PAH. Although no specific subgroup analysis is provided, improvement was apparently mainly in patients with IPAH. In a smaller single centre clinical trial, adding sildenafil to patients with IPAH or SSc-PAH after they failed initial monotherapy with bosentan, demonstrated that combination therapy improved the 6MWD and functional class in IPAH patients. The outcome in patients with SSc-PAH was less favourable, although combination therapy may have halted clinical deterioration. Importantly, there were more side-effects reported in the SSc-PAH compared with the IPAH patients, including hepatotoxicity that developed after addition of sildenafil to bosentan monotherapy [111].

## Anticoagulation

The rationale and recommendation for the use of anticoagulation in severe PAH is based on pathologic evidence of pulmonary thromboembolic arterial disease and thrombosis *in situ* in patients with IPAH [112], and a few non-randomised or retrospective clinical studies [83, 113] demonstrating a significant beneficial effect of anticoagulation on survival in IPAH. The rationale for anticoagulation in other forms of PAH, in particular in SSc-PAH or other forms of CTD is even less sound. Theoretically, there is potential for increased bleeding in patients with CTD, particularly with SSc in whom gastric antral vascular ectasia may be common.

An unpublished review of our experience with anticoagulation in over 100 patients with SSc-PAH suggests that less than 50% of these patients remain on long-term anticoagulation therapy, mainly because of the occurrence of occult bleeding in the gastro-intestinal tract, the source of which is often very difficult to diagnose (unpublished data).

### Tyrosine kinase inhibitors

A pathological hallmark of PAH is aberrant proliferation of endothelial and smooth muscle cells and fibroblasts which, combined with an increased expression of secreted growth factors such as VEGF and basic fibroblast growth factor (bFGF), has caused a paradigm shift in treatment strategies. Some investigators have even linked this condition to a neoplastic process reminiscent of advanced solid tumours [114]. As a result, anti-neoplastic drugs have been tested over the past few years in experimental models [115, 116] and in some patients [117, 118], with two essential strategies: disruption of the PDGF or the VEGF signalling pathway. A proof of concept, phase II, multicentre trial to evaluate the safety, tolerability and efficacy of imatinib in patients with PAH recently demonstrated that imatinib is well tolerated. However, there was no significant change in 6MWD (primary end-point) although there was a significant decrease in PVR and an increase in cardiac output in imatinib-treated patients compared with placebo [119]. Whether these new anti-neoplastic drugs with anti-tyrosine kinase activity will have a role in CTD-PAH, particularly SSc-PAH, remains to be determined. It is noteworthy that RV function improved significantly in response to imatinib treatment in a single case report of SSc-PAH [120]. In a very small open label phase I/IIa pilot trial of imatinib treatment for SSc-related ILD, there were significant side-effects of the drug without evidence of significant improvement in pulmonary function tests (PFTs) [121]. Other tyrosine kinase inhibitors (TKIs) (targeting VEGF, PDGF, or EGF receptors) may perhaps be effective for SSc-related complications; however, these should be tested in carefully controlled trials [122].

### Lung transplantation

Lung transplantation is offered as a last resort to patients with PAH who fail medical therapy. However, CTD-PAH patients often have associated morbidity and organ dysfunction other than the lung that place them at a specifically high risk for this procedure. As an example, the post-operative potential of aspiration due to gastro-oesophageal reflux combined with intrinsic oesophageal dysmotility may place the transplanted organ at increased risk. For these reasons, patients with SSc-PAH are sometimes denied the lung transplant option in some centres, although the results of two studies in SSc patients [123, 124] suggest that lung transplantation, in carefully selected patients, is a viable therapeutic option for these patients. Lung transplant experts now suggest that candidates for transplantation should be evaluated on an individual basis.

## Animal models of SSc-PAH

Animal models are of great utility to identify molecular key players and potential therapeutic targets and for preclinical proof of concept studies in SSc-PAH. Unfortunately, there is a lack of well characterised and validated animal models of SSc that mimic complications of SSc such as ILD and/or pulmonary vasculopathy [125].

The UCD200/206 chicken model [30] was the first SSc animal of vasculopathy, however, to date, due to the drawbacks of chicken housing and hatching, rodent models are preferred. So far, there are three SSc animal models with an additional vascular phenotype. The caveolin-1 knockout mice develop both pulmonary vasculopathy and fibrosis in the context of increased TGF-β signalling [126]. The transgenic (tg) mouse strain Tbeta RIIDeltak-fib, characterised by balanced ligand-dependent upregulation of TGF-β signalling, provides insights into the altered biomechanical properties of large elastic arteries in human SSc in the context of perturbed TGF-β and ET activity [127]. However, in both models, pulmonary vasculopathy has not been evaluated in detail.

The Fra-2 (Fos-related antigen-2) tg mouse model combines vasculopathy with fibrosis of the skin and internal organs, and Fra-2 protein is overexpressed in the skin and lungs of patients with SSc [31, 128]. In these animals, most of the characteristic pathologic features of SSc-PAH could be observed, except for PVOD-like lesions which were absent. Additionally, interstitial inflammation and fibrosis occurred, closely resembling human nonspecific interstitial pneumonia (NSIP) as the most common form of ILD in SSc patients [129]. When assessing potential molecular key players of vascular remodelling, the PDGF signalling axis was found to be activated which is consistent with human data on IPAH [130] and SSc-PAH [22]. To test the model's response to treatment, a subgroup of Fra-2 tg mice was treated with the TKI nilotinib which inhibits both TGF-β and PDGF signalling pathways. Nilotinib is an orally administered second-generation TKI with a superior toxicity profile that was developed for patients with treatment refractory CML or with intolerance to imatinib. Similar to imatinib, nilotinib inhibited the development of fibrosis in preclinical models of SSc [131]. In Fra-2 tg mice, treatment with nilotinib had striking effects since it completely prevented vascular remodelling and remarkably reduced the development of interstitial lung fibrosis. Thus, Fra-2 tg mice might represent the first preclinical model of SSc-PAH [132].

## Novel targets for therapy of SSc-PAH and SSc-PH

Since SSc-PAH differs from IPAH, further studies are needed to define whether the key molecules identified in IPAH might also play a role in the pathogenesis of SSc-PAH, especially since at least at subclinical level tissue fibrosis and inflammation might be more prevalent. Thus, the ideal drug should simultaneously target both pulmonary vascular and fibrotic changes which might also apply to SSc-PH due to ILD.

TGF-β and PDGF are key players in the development of fibrosis and vasculopathy in SSc, and since both molecules signal through tyrosine kinases, TKIs have become of major interest as potential anti-fibrotic agents. In SSc, larger prospective and partially controlled trials on imatinib have been initiated [121, 133], and so far, moderate but significant effects on skin and lung fibrosis have been reported [133], whereas in a randomised, placebo-controlled, double-blind trial in patients with mild-to-moderate idiopathic pulmonary fibrosis (IPF), no effect on survival or clinical outcome measures such as lung function could be observed [134]. However, another TKI, BIBF 1120, which targets PDGF, VEGF, and fibroblast growth factor (FGF) receptors, was recently tested in a phase II trial in patients with IPF, and compared with placebo treatment, a trend toward a reduction in the decline in lung function could be observed [135]. In IPAH, the PDGF, and in particular the PDGF-BB pathways are activated, especially in vascular cells and perivascular inflammatory cells [130]. Interestingly, PDGF receptor (PDGFR)-β immunoreactivity is more common in the pulmonary vessels of patients with SSc-PAH compared with IPAH [22]. The recent findings from the Fra-2 tg mouse model, where PDGF-BB signalling is activated and treatment with nilotinib prevents vascular remodelling and development of lung fibrosis [132], additionally support a potential role for TKIs in patients with SSc-PAH.

Furthermore, since Fra-2 has been found to be overexpressed in the skin and lungs of SSc patients [31, 128], Fra-2 as part of the activator protein (AP)-1 complex might itself represent a potential future therapeutic target in SSc. Based on previous data on microvasculopathy and dermal fibrosis in SSc patients [31, 80, 81], a recent study demonstrated substantial anti-fibrotic effects of AP-1 inhibition in different animal models of SSc [136]. Thus, Fra-2/AP-1 might represent an additional relevant molecular target for future SSc-specific therapies.

The role of 5-hydroxytryptamine (5-HT) signalling in the pathogenesis of IPAH has long been established [137, 138], and in animal models of IPAH substantial effects on vascular remodelling were observed [139, 140]. Recent data additionally suggested an important role in the development of IPF [141, 142]. In SSc, the pathogenic implication of 5-HT signalling pathways has only recently been studied in detail [143]. 5-HT is released upon activation of platelets due to microvascular injury. Since blood levels are elevated in SSc patients, it is hypothesised that 5-HT

might link vascular injury and fibrosis in SSc. *In vitro*, 5-HT strongly induces the synthesis of extracellular matrix proteins in dermal fibroblasts *via* activation of 5-HT2B receptors (5-HTR2B) in a TGF-β-dependent manner. *In vivo*, 5-HT deficiency or inhibition by 5-HT2 inhibitors reduced dermal fibrosis both in inducible and genetic models of fibrosis. Thus, these recent findings in SSc and the previous data on IPAH and IPF suggest 5-HT/5-HT2B signalling as a potential molecular target to simultaneously treat vascular remodelling and fibrosis in SSc. Terguride, a potent 5-HT2A and 5-HT2B inhibitor already approved for the treatment of ovulation disorders caused by hyperprolactinemia and hyperprolactemic pituitary adenoma, seems a promising drug to test in SSc-PAH. Since terguride acts as a non-surmountable 5-HT2B antagonist, there are few concerns regarding potential negative side effects such as those seen in chronic treatment with ergoline derivatives (*e.g.* pergolide, cabergoline) or with anorexic drugs (*e.g.* fenfluramine) which have caused retroperitoneal, pleural and pericardial fibrosis as well as valvular heart disease due to their 5-HT2B agonist activity.

Finally, given the emerging role of IL-6 in SSc and PH [8, 19, 144, 145], the clinically approved IL-6 antagonist, tocilizumab, might also be considered a future treatment option, although further preclinical and clinical studies are needed to address the role of IL-6 in SSc-PAH. So far, there are only single case reports on the use of tocilizumab in a patient with MCTD-PAH [146] and PAH in Castleman's disease [147].

## Conclusion

PH is a common complication of CTD, particularly SSc where outcome is significantly worse compared with other diseases (such as IPAH). In addition, modern therapy for PAH appears to be of limited value in SSc-PAH. Similarly, currently available markers of disease onset (in a population at risk), disease severity or response to therapy in SSc-PAH and other CTD are either limited or lacking. Care of these complex patients calls for a multidisciplinary approach in order to ensure comprehensive therapy and monitoring [18]. Whether early diagnosis and treatment of SSc-PAH patients improves outcomes is still uncertain and needs to be confirmed in properly designed studies. Finally, there is a pressing need to identify potential genetic causes and establish novel physiologic, molecular, and imaging biomarkers that will improve the understanding of the pathogenesis of this disease and potentially serve as reliable tools to monitor therapy in this devastating syndrome.

### *Statement of Interest*

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# Chapter 5

# Portopulmonary hypertension: a consequence of portal hypertension

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**SUMMARY: Portopulmonary hypertension (POPH) is an uncommon pulmonary vascular consequence of portal hypertension. It presents as exertional dyspnoea and may lead to right heart failure and death if untreated. There is no relationship between the existence and degree of POPH and the severity of advanced liver disease. Due to the spectrum of pulmonary haemodynamic changes associated with hepatic dysfunction, screening by transthoracic echocardiography and confirmation by right heart catheterisation (RHC) is necessary for accurate diagnosis and therapeutic considerations. Despite the lack of controlled studies, pulmonary vasomodulation therapies in POPH can significantly improve pulmonary haemodynamics and right ventricular (RV) function. The potential to "cure" POPH, at least haemodynamically, with a combination of pulmonary vasomodulation therapy and liver transplantation appears to be an attainable goal in a cohort of POPH patients yet to be optimally characterised. Controlled, multicentre studies and long-term follow-up post-liver transplantation are needed.**

**KEYWORDS: Echocardiography, liver transplant, right heart catheterisation**

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The existence of pulmonary arterial hypertension (PAH) in the setting of advanced liver disease is well known and recognised internationally [1]. Because the pathophysiology of advanced liver disease results in portal hypertension and arguably nearly all cases of PAH follow the development of portal hypertension, clinicians have invoked the term "portopulmonary hypertension" (POPH). The therapeutic advances in treating PAH, specific effects of treating POPH and the potential outcomes of liver transplant in the setting of POPH have stimulated ongoing interest and raised the importance of this syndrome. This chapter emphasises recent large series, single-site clinical observations and the outcome data from both French [2] and US-based registries [3] of POPH patients.

## Diagnostic criteria and severity of POPH

Diagnostic criteria and classification of POPH severity based upon right heart catheterisation (RHC) are necessary due to the various pulmonary haemodynamic patterns that complicate advanced liver disease [4, 5]. Identifying which patients have POPH, deciding who needs pulmonary vasomodulation therapy and determining the risks and timing for potential liver transplant are clinical issues based upon RHC (table 1). The vascular pathology that characterises POPH includes obstruction to arterial flow due to vasoconstriction, endothelial and smooth muscle proliferation, *in situ* thrombosis and plexogenic arteriopathy [6, 7]. However, all-cause pulmonary hypertension (PH) is not uncommon in association with portal hypertension, reflecting: 1) the effects of a hyperdynamic circulatory state induced by liver dysfunction; 2) excess pulmonary venous volume due to diastolic dysfunction and/or renal insufficiency; and 3) true PAH due to vascular obstruction [6]. The distinctions are haemodynamically important and have significant therapeutic implications, as shown in figure 1.

Transthoracic echocardiography (TTE) is the most practical screening method to detect POPH [8–10]. By assessing the tricuspid regurgitation peak velocity, estimating the right atrial pressure ($P_{ra}$) by inferior vena cava changes with inspiration, and using the modified Bernoulli equation, an estimate of right ventricle (RV) systolic pressure (*i.e.* pulmonary artery systolic pressure ($sP_{pa}$)) can be determined in ~80% of patients with portal hypertension [10]. This quantitative approach allows one to decide which patients should precede to RHC for the definitive characterisation of pulmonary haemodynamics. A RV systolic pressure of >50 mmHg has been the cut-off criteria to proceed to RHC in the current Mayo Clinic (Rochester, MN, USA) algorithm followed since 1996 [4]; rarely immeasurable tricuspid regurgitation with abnormal qualitative RV size or function results in RHC. TTE was noted to have 97% sensitivity and 77% specificity to detect moderate-to-severe PAH prior to liver transplantation [10].

PAH from any cause, including POPH, is defined by a mean pulmonary artery pressure (mean $P_{pa}$) of >25 mmHg and pulmonary capillary wedge pressure ($P_{pcw}$) of <15 mmHg. Those POPH patients with a mean $P_{pa}$ of >35 mmHg are particularly vulnerable to poor outcomes with attempted liver transplantation, especially if there is no attempt to treat the POPH with current pulmonary vasomodulating medications [11]. With current treatments, POPH outcomes are variable, yet in highly selected POPH patients, with aggressive treatment and successful liver transplant, pulmonary haemodynamics may completely normalise. RV size and function normalises and liberation from pulmonary vasomodulation medications may be allowed.

Importantly, POPH should be distinguished from the other major pulmonary vascular consequences of liver disease, namely hepatopulmonary syndrome (HPS) [5, 12]. In that syndrome, arterial

**Table 1.** Diagnostic and severity criteria for portopulmonary hypertension

| Variable | Criterion |
|---|---|
| **Portal hypertension** | Clinical diagnosis (ascites, varices, splenomegaly) |
| **Mean $P_{pa}$** | >25 mmHg |
| **PVR**[#] | >240 dyn·s·cm$^{-5}$ |
| **TPG**[¶] | > 12 mmHg |
| **Degree of severity** | |
| Mild | 25< mean $P_{pa}$ <35 mmHg |
| Moderate | 35⩽ mean $P_{pa}$ ⩽45 mmHg |
| Severe | 45 mmHg ⩽ mean $P_{pa}$ |

$P_{pa}$: pulmonary artery pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary gradient. [#]: PVR = (mean $P_{pa}$ – $P_{pcw}$) × 80/CO, where $P_{pcw}$ is pulmonary capillary wedge pressure and CO is cardiac output. [¶]: where $P_{pcw}$ is >15 mmHg (abnormal), an abnormal TPG (mean $P_{pa}$ – $P_{pcw}$) distinguishes between simple volume excess causing increased mean $P_{pa}$ and the pulmonary artery vasculopathy that characterises portopulmonary hypertension.

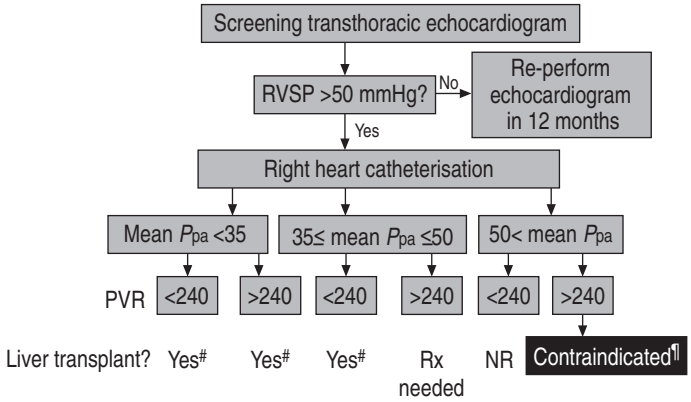



**Figure 1.** Current portopulmonary hypertension evaluation and treatment algorithm used at the Mayo Clinic (Rochester, MN, USA). RVSP: right ventricular systolic pressure; $P_{pa}$: pulmonary artery pressure; PVR: pulmonary vascular resistance; Rx: vasoremodelling treatment advised prior to liver transplantation (prostacyclin with or without ambrisentan); NR: never reported. #: risk of proceeding with liver transplantation is minimal; ¶: high risk of intraoperative event at graft reperfusion, case cancelled.

hypoxaemia is caused by intrapulmonary vascular dilatations (exactly opposite to the vascular obstructions documented in POPH) that form as a remodelling process (angiogenesis) due to factors yet to be identified. In addition, the pulmonary haemodynamics associated with HPS reflect a normal pulmonary vascular resistance and usually a high-flow state characterised by an increased cardiac output. The distinction is quite important, especially if liver transplantation is to be considered, because of the differences in risk and outcome between these two syndromes (table 2) [12].

## Clinical manifestations

Dyspnoea on exertion, at rest or both is the predominant presenting symptom; chest pain and syncope are symptoms suggestive of severe POPH [13]. Since other reasons for dyspnoea may include ascites, anaemia, fluid retention and muscle wasting (all manifestations of advanced liver disease), the consideration of POPH as a diagnosis may be overlooked. On physical examination of the heart, the presence of hyperdynamic precordium, an accentuated second heart sound (best heard at the apex) reflecting forceful closure of the pulmonic valve due to high $P_{pa}$, and a systolic murmur during RV systolic function due to tricuspid valve regurgitation may be noted. With severe POPH there may be marked distension of the jugular veins, peripheral oedema, ascities and a RV third heart sound. Lung examination is usually normal and clubbing or cyanosis (as seen in HPS) is quite uncommon. Mild hypoxaemia is common and often associated with abnormal overnight pulse oximetry. Rarely is severe hypoxaemia documented, as opposed to being commonly seen in HPS [13].

The chest radiograph usually demonstrates cardiomegaly and enlargement of the central pulmonary arteries as the duration and severity of POPH progresses (usually over many months) [13]. The electrocardiogram may show rightward electrical axis, right bundle branch block pattern and, when POPH is severe, the presence of inverted T-waves in the precordial V1–V4 leads can be seen. Although rare, it is important to rule out chronic pulmonary emboli as a cause of PAH even in the setting of liver disease, especially with portal vein and hepatic vein thromboses.

Pulmonary function tests are usually not helpful in diagnosis or management, since a common abnormality seen in PAH, a reduced single breath diffusing capacity, is frequently seen in most patients with advanced liver disease.

A recent study suggested that autoimmune liver disorders (primary biliary cirrhosis and cirrhosis from autoimmune hepatitis) and female sex are more frequently associated with POPH [14]. Although mainly affecting adults, POPH has been reported in the paediatric age group [13]. The presence of spontaneous portocaval shunts is more frequent in those with POPH; patients with previous surgical portocaval shunts have a high frequency of POPH years after surgery [15–17]. Splenectomy accomplished during portocaval shunt surgery may also be a risk factor for POPH [18]. Other disorders that affect the liver may cause PH. Of particular concern is Rendu–Osler–Weber syndrome, also called hereditary haemorrhagic telangiectasia (HHT) [19]. In this

**Table 2.** Distinctions between portopulmonary hypertension and hepatopulmonary syndrome

| Variable | Portopulmonary hypertension | Hepatopulmonary syndrome |
|---|---|---|
| **Presentation** | | |
| Paediatric | Rare | Yes |
| Adult | Most common | Yes |
| **Symptoms** | Exertional dyspnoea, chest pain/syncope | Exertional dyspnoea |
| **Clinical exam** | Increased second heart sound, systolic murmur | Clubbing/cyanosis, systolic murmur |
| **Genetic predisposition** | Yes | Unknown |
| **Liver diseases** | Autoimmune (common) | No relation |
| **Portocaval shunts** | Spontaneous (common) | No relation |
| **CTP classes** | No relation | No relation |
| **MELD scores** | No relation | No relation |
| **Lung biopsies** | Not indicated | Not indicated |
| **Chest radiograph** | Cardiomegaly, enlarged central arteries | Normal |
| **Re-performed echocardiogram** | RBBB, T-wave inversion V1–V4 | Normal |
| **Electrocardiogram** | | |
| **Transthoracic echocardiogram** | Increased RV size; reduced RV function plus shunt | Normal RV, increased shunt |
| **Arterial hypoxaemia** | Mild | May be severe |
| **Abnormal overnight oximetry** | Common | Common |
| **Pulmonary haemodynamics** | Increased mean $P_{pa}$; increased PVR | Increased mean $P_{pa}$; normal PVR |
| **Pulmonary angiography (common)** | Enlarged central arteries, distal pruning | Spongy appearance, discrete AV communications (uncommon) |
| **Liver transplant** | MELD exception. If mean $P_{pa}$, <35 mmHg and PVR <400 dyn·s·cm$^{-5}$ | MELD exception. If $P_{a,O_2}$ <60 mmHg |
| **Causes of death** | Right heart failure, GI complications | GI complications |

CTP: Childs–Turcotte–Pugh; MELD: Model for End Stage Liver Disease; RBBB: right bundle branch block; RV: right ventricle; $P_{pa}$: pulmonary artery pressure; PVR: pulmonary vascular resistance; AV: arteriovenous; GI: gastro-intestinal.

syndrome, there can be numerous intrahepatic arteriovenous communications within the liver causing a high-flow state (with normal pulmonary vascular resistance (PVR) and leading to right heart failure). Liver transplant can ameliorate right heart failure, as well as reduce the frequency and severity of epistaxis [19]. Finally, there appears to be no relationship with the existence or severity of POPH, or with the severity of liver dysfunction as characterised by the Childs–Turcotte–Pugh (CTP) or the Model for End Stage Liver Disease (MELD) scores [13, 20].

Important similarities and differences between POPH and other phenotypes of PAH exist. Compared with idiopathic PAH (IPAH), POPH is characterised by higher cardiac outputs and is generally less severe, as measured by mean $P_{pa}$ and PVR (outcomes are summarised later) [3, 21]. In addition, it is not infrequent for POPH patients to have histories of splenectomy, which may be an independent factor for developing PAH [18]. Finally, it is not uncommon for patients to have an initial diagnosis of IPAH but then later determine because of thrombocytopenia and other imaging (even in the setting of normal liver function tests) that portal hypertension exists and POPH is the correct diagnosis.

## Prevalence and natural history

It is unclear who coined the term ''portopulmonary hypertension'', but YOSHIDA *et al.* [22] appear to have been the first authors to use the term in 1993, as they described the first successful case of

POPH (a 39-year-old male with long-standing chronic active hepatitis) to undergo successful liver transplantation. The first clinical and pathological report of what we now know as POPH was probably provided by MANTZ and CRAIGE [23] in 1951. They described the necropsy results of a 53-year-old female with spontaneous portocaval shunt (due to a probable congenital portal vein narrowing) that originated at the confluence of the portal, splenic and mesenteric vein, coursed through to the mediastinum and was lined by varying amounts of thrombus thought to have embolised *via* the innominate vein into the right heart and pulmonary arteries. In addition to embolised small pulmonary arteries, an extreme endothelial proliferation and recanalisation process was documented. Subsequently, several small series and case reports with autopsy results have described pulmonary arterial obstruction and pulmonary plexogenic arteriopathy with and without thromboemboli [7, 24–27]. Therefore, two distinct pulmonary vascular obstructive patterns causing PAH in association with portal hypertension may well exist: 1) chronic pulmonary emboli from spontaneous or surgical portocaval shunts and/or *in situ* thrombus; and 2) a vasoconstrictive, proliferative endothelial/smooth muscle process due to circulating mediators that bypass normal hepatic metabolism due to flow patterns of portal hypertension.

Large series have confirmed the coexistence of these portal and pulmonary vascular abnormalities is not coincidental. An unselected series of 17,901 patients demonstrated that PAH associated with cirrhosis was more than five times more frequent than PAH without cirrhosis [28]. Within the 1981–1987 National Institutes of Health (NIH) national registry of "primary" PH from 32 centres reported by RICH *et al.* [29], additional analyses by GROVES *et al.* [30] concluded that 8.3% were likely to have had POPH (17 out of 204; 187 had PPH). HADENGUE *et al.* [20] reported the largest prospective study of patients with portal hypertension (n=507) in which portopulmonary haemodynamic measurements concluded that 2% had POPH.

With the advent of pulmonary vasomodulation drugs and liver transplantation, prospective studies have focused on the frequency of POPH in clinic settings, national registries and individual transplant centre experiences. HUMBERT *et al.* [2] reported a 10.4% frequency of POPH (70 out of 674) from the pulmonary hypertension registry clinics of 17 French university hospitals over a 12-month period (2002–2003). The US-based Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) documented a 5.3% POPH frequency (174 out of 3,525) in which there were 68% prevalent and 32% incident cases satisfying the criteria that mean $P_{pa}$ >25 mmHg and PVR >240 dyn·s·cm$^{-5}$ with $P_{pcw}$ <15 mmHg [3]. Of interest were the additional 29 patients who satisfied mean $P_{pa}$ and PVR criteria, but whose $P_{pcw}$ was >15 mmHg; each of those patients had a transpulmonary gradient of >12 mmHg (abnormal). Their outcome data were analysed separately. Following slightly different PVR diagnostic criteria as part of outpatient RHC diagnostic assessments, the largest POPH–liver transplant centre experiences reported to date documented frequencies of 8.5% (Baylor Medical Center, Dallas TX, USA: 102 out of 1,205; PVR >120 dyn·s·cm$^{-5}$), 6.1% (Clamart, France: 10 out of 165; PVR > 120 dyn·s·cm$^{-5}$), and 5.3% (Mayo Clinic: 66 out of 1,235; PVR >240 dyn·s·cm$^{-5}$) of POPH in patients considered for liver transplantation [4, 31, 32].

The natural history of POPH has been confounded by small series performed in a period when none of the current pulmonary vasomodulating therapies was available *versus* the current era, with the evolving pulmonary vasomodulation therapies and liver transplant experiences. ROBALINO and MOODIE [33] reported a dismal 5-year survival of 4% (n=78) in an era before continuous IV prostacyclin infusion was available. SWANSON *et al.* [34] reported a 14% (n=19) 5-year survival in POPH patients denied liver transplant and not treated with any of the current pulmonary vasomodulation therapies. At the French National Centre for PAH, Clamart, France (n=154 over a 20-year span until 2004), LE PAVEC *et al.* [35] described 1-, 3- and 5-year survivals of 88, 75 and 68%, respectively, in POPH patients (but mainly Child's class A and alcoholic cirrhotics). Pulmonary vasomodulating therapies were given to 45 (29%) out of 154 patients; severity of cirrhosis and low cardiac output were associated with poor outcome. Causes of death in all series mentioned herein were equally distributed between right heart failure due to POPH and direct complications of liver disease (bleeding, sepsis, hepatocellular carcinoma).

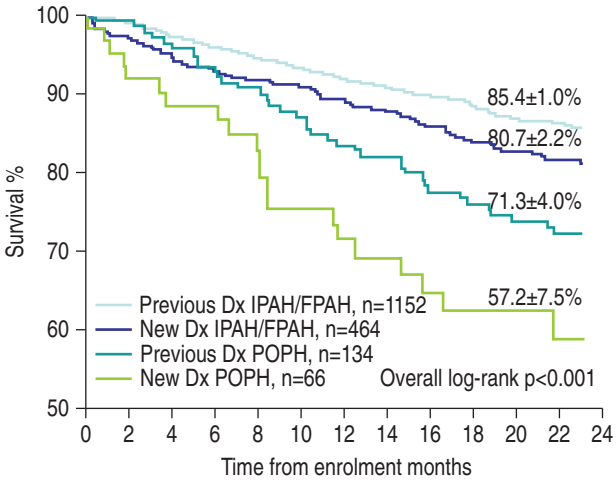
In the REVEAL registry, two important POPH observations were reported [3]. First, POPH treatment patterns reported in the REVEAL registry demonstrated that the use of any pulmonary vasomodulation therapy for POPH was delayed compared with patients diagnosed with IPAH. Specifically, at the time of entry into the registry, only 25% were on pulmonary vasomodulation therapy; by the end of 12 months' follow-up, 74% of those alive were on treatment. Secondly, although baseline haemodynamics in POPH were significantly better than those with IPAH, the 1- and 3-year survivals were worse (fig. 2); the 5-year survival for all POPH patients was 40 *versus* 64% for IPAH. Liver disease aetiologies and causes of death were not determined in the registry. Survival was not analysed by the type of pulmonary vasomodulation therapy.

There are two important caveats when characterising the natural history of POPH. First, with the advent of pulmonary vasomodulating therapies, every controlled, multicentre study has excluded POPH patients. This universal exclusion in the US further complicates the understanding of POPH outcomes compared with other PAH disorders. Secondly, from 2002 in the USA, a higher priority of liver transplantation was an option for highly selected patients with POPH [36]. Formalisation of higher priority pulmonary haemodynamic criteria was put forth in 2006 and was standardised in 2010. Only patients with moderate-to-severe POPH (mean $P_{pa}$ >35 mmHg) who attained significant haemodynamic improvement with pulmonary vasomodulation therapy (mean $P_{pa}$ <35 mmHg and PVR <400 dyn·s·cm$^{-5}$) were granted higher priority for liver transplantation. From 2002 to 2010, 155 POPH patients were granted such priority by regional review boards [37].

## Pathobiology

POPH is indistinguishable from the histopathology of other PAH phenotypes [6, 7]. Based upon autopsy and lung explant studies, POPH is characterised by a spectrum of obstructive and remodelling changes in the pulmonary arterial bed. Initially, medial hypertrophy with smooth muscle proliferation and a transition to myofibroblasts has been documented. Intuitively, this vasoconstrictive process could be responsive to pulmonary vasodilator therapy. As this proliferative pathologic process progresses, the addition of platelet aggregates, *in situ* thrombosis and intimal fibrosis create sporadic, web-shaped lesions that impede pulmonary arterial blood [6, 7]. This web-like pathology is termed "plexogenic arteriopathy" and it is unknown whether such structures are irreversible [7].

The factors leading to such pulmonary vascular obstruction in the setting of liver disease are complex but originate from the development of portal hypertension. Pulmonary vascular pathology occurs within the context of a hyperdynamic state caused by extrahepatic (splanchnic) vasodilation [13]. It is unknown if this persistent high-flow state initiates (by shear stress) or exacerbates (in combination with circulating mediators) the pulmonary vascular proliferative process. Genetic




**At risk n**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Previous Dx IPAH/FPAH | 1152 | 1145 | 1124 | 1107 | 1089 | 1065 | 1051 | 1031 | 1014 | 1005 | 969 | 958 | 946 |
| New Dx IPAH/FPAH | 464 | 437 | 396 | 388 | 350 | 318 | 311 | 286 | 257 | 250 | 226 | 205 | 200 |

**Figure 2.** Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) 2-year survival patterns for portopulmonary hypertension (POPH) and idiopathic pulmonary arterial hypertension (IPAH) categorised by previous diagnosis *versus* newly diagnosed at the time of entry into the registry. Dx: diagnosis; FPAH: familial pulmonary arterial hypertension. Reproduced and modified from [3] with permission from the publisher.

predisposition may also play a role since not all patients with portal hypertension develop POPH [38]. It has been demonstrated that the pulmonary endothelial cells lack prostacyclin synthase in POPH patients (hence a lack of prostacyclin vasodilation) [39], and that the pulmonary vascular bed is exposed to increased levels of circulating endothlin (ET)-1 in the setting of cirrhosis (a potent vasoconstrictor and facilitator of smooth muscle proliferation) [40, 41] and may be deficient in local nitric oxide (NO) effect (for vasodilation) [42]. The role of other circulating and receptor factors that may affect the pulmonary endothelium is speculative. These factors include vasoconstrictive/proliferative mediators, such as serotonin, thromboxane, vasoactive intestinal peptide and vascular endothelial growth factor (VEGF), as well as the possible imbalance of endothelin receptors ($ET_A$ mediating vasoconstriction and $ET_B$ mediating vasodilation) in the pulmonary arterial bed [42]. The mechanistic link between oestrogen signalling, serum oestradiol levels, circulating endothelial progenitor cells and the development of POPH is a current research hypothesis of interest [43, 44].

It is hypothesised that, initially, intrahepatic injury leads to an intrahepatic increased resistance to flow. Such injury evokes mediators that cause splanchnic vasodilation *via* enhanced local NO affect and presumed angiogenesis affect [13, 45]. The splanchnic bed becomes hyporesponsive to vasoconstrictors; excess volume occurs due to renal retention and a hyperdynamic state is generated. This high flow exacerbates the existing portal hypertension due to increased intrahepatic resistance to flow, leading to the creation of alternative flow pathways: portocaval shunts and oesophagogastric varices. Presumably, such aberrant pathways allow other mediators to reach the pulmonary arterial bed and, in the setting of high flow, ''trigger'' the pulmonary arterial proliferative process.

Therefore, in POPH, the resulting pulmonary haemodynamics have been well described: increased mean $P_{pa}$, high cardiac output, normal $P_{pcw}$, but an increased calculated PVR to the proliferative, obstructive process in the pulmonary arterial bed. Note that if the pulmonary vascular pathologic proliferative process does not occur, only a high-flow state exists, with no obstruction to flow and with resulting normal calculated PVR. Marked excess volume due to fluid retention may occur and be reflected by increased $P_{pcw}$. Depending on the existence of proliferation and the degree of such fluid retention, an increase in both PVR and $P_{pcw}$ can confuse the interpretation of pulmonary haemodynamics [4]. In that scenario, which may occur in up to 25% POPH patients, the existence of obstruction to pulmonary arterial flow is manifest by an increased transpulmonary gradient (mean $P_{pa} - P_{pcw} > 12$ mmHg). These patients should not be excluded from the diagnosis of POPH due to high $P_{pcw}$ alone.

As the pulmonary vasoproliferative process progresses, the increasing resistance to flow will at some point begin to restrict the degree of cardiac output flowing through the pulmonary vascular bed. Strain on the RV will be seen with dilation of the RV and reduction in systolic function (as measured by reduced longitudinal contractility). Progressive reduction in cardiac output will then evolve with right heart failure, leading to hepatic venous engorgement and worsening portal hypertension. Death from either right heart failure or portal hypertension complications will occur if no pulmonary vasomodulating therapeutic intervention is attempted [13].

## Medical treatment

The immediate goal of pulmonary vasomodulation treatment for POPH is to improve pulmonary haemodynamics by reducing the obstruction to pulmonary arterial flow. This can be accomplished using medications that selectively or in combination result in vasodilation, antiplatelet aggregate and antiproliferation effects [13]. These goals may be attained by augmenting the lack of pulmonary endothelial prostacyclin synthase deficiency (prostacyclin infusion), blocking circulating ET-1 effects (endothelin receptor antagonists (ERA)) and enhancing local NO vasodilatation effects (phosphodiesterase inhibitors) [13]. The ultimate goal, in addition to favourably affecting pulmonary haemodynamics (decrease mean $P_{pa}$, decrease PVR and increase cardiac output), is to stabilise, improve or normalise RV function.

**Table 3.** Liver transplant outcomes in the setting of portopulmonary hypertension (POPH)

| Outcome | [Ref.] |
|---|---|
| **POPH waiting-list mortality** | [32, 46–48] |
| **POPH MELD exception pre-liver transplant** | [37, 46] |
| **Case cancelled in operating room** | [11, 31, 49, 50] |
| **Intraoperative death** | [11, 31, 34, 35, 37, 51] |
| **Transplant hospitalisation death** | [11, 31, 37, 51–56] |
| **POPH post-liver transplant** | |
| Resolved; pulmonary vasomodulation discontinued | [37, 46–49, 57–61¶] |
| Resolved/stable without pulmonary vasomodulation | [22, 32, 52, 53, 62] |
| Improved/stabilised/pulmonary vasomodulation continued | [37, 46, 47+, 57+, 58+, 63, 64, 65+] |
| Progressive despite pulmonary vasomodulation | [31] |
| **Late death not due to POPH** | [31, 34, 52] |
| **Late death due to POPH** | [31, 35] |
| **Multiorgan (heart–lung–liver; lung–liver transplant)#** | [66, 67] |
| ***De novo* PAH post-liver transplant** | [68§] |

MELD: Model for End stage Liver Disease; PAH: pulmonary arterial hypertension. #: multiorgan transplants have been reported in the literature for cystic fibrosis, $\alpha_1$-antitrypsin deficiency and sarcoidosis, but these entities also affect lung parenchyma and many cases were accomplished in a period prior to current pulmonary vasomodulation medications and therefore have not been included; ¶: living donor liver transplant (three patients); +: combined pulmonary vasomodulating medication use; §: a literature review of 13 such cases.

Uncontrolled small series and recent case reports have demonstrated that pulmonary vasomodulation therapies used for other types of PAH could be beneficial for patients with POPH (table 3) [46–49, 52, 57–59, 63, 64, 69–75,]. It is important to stress that improvements in both mean $P_{pa}$ and PVR are the goals in treating POPH. However, mean $P_{pa}$ may not decrease as much as desired, because increases in cardiac output associated with reduced obstruction to flow (measured by decreased PVR) will result in higher flow (and subsequent pressure).

### *Prostacyclins*

The most dramatic pulmonary vasomodulation effects in POPH have been seen with the use of continuous prostacyclin infusion *via* a central catheter and oral ERAs. In a summary of 48 patients treated with intravenous epoprostenol from five studies, mean $P_{pa}$ decreased by 25% (48 to 36 mmHg), PVR decreased by 52% (550 to 262 dyn·s·cm$^{-5}$) and cardiac output increased by 38% (6.3 to 8.7 L·min$^{-1}$) (all $p<0.01$) [13, 46, 47, 49, 52, 69]. Other prostacyclins (*i.v.* treprostinil and inhaled iloprost) have resulted in significant pulmonary haemodynamic improvement in POPH [57, 58, 70].

### *Endothelin receptor antagonists*

Regarding the use of ERAs, HOEPER *et al.* [71] documented 1- and 3-year survivals of 94 and 89% in 18 patients with POPH and Child's A-severity liver disease using the nonselective ERA bosentan. No liver toxicity was noted. However, ERIKSSON *et al.* [72] correctly warned about potential liver toxicity with the use of bosentan, occurring in up to 10% of patients without documented POPH. Although KAEHLER *et al.* [73] reported success in POPH with the use of a selective ETA antagonist, sitaxentan, this medication has not been approved in the US and has been associated with fatal hepatic failure. CARTIN-CEBA *et al.* [59] reported 13 POPH patients using the ETA antagonist ambrisentan (10 mg daily) and documented improvement in each of eight POPH patients at 1 year (mean $P_{pa}$ 58 to 41 mmHg and PVR 445 to 174 dyn·s·cm$^{-5}$; $p=0.004$); it is noteworthy that five out of eight patients normalised their PVR. In further support of ambrisentan in POPH, HALANK *et al.* [74] described significant improvement in both exercise capacity and symptoms in 14 POPH patients. Importantly, neither of the uncontrolled ambrisentan use studies was associated with hepatic toxicity. This may be due to the differences in chemical structure (ambrisentan: propionic acid; bosentan and sitaxentan: sulfur base) and distinct hepatic metabolic pathways [75].

### *Phosphodiesterase inhibitors*

The use of phosphosdiesterase inhibition (sildenafil) to enhance the NO vasodilating effect either alone or in combination with other pulmonary vasomodulation therapies has successfully improved POPH pulmonary haemodynamics and facilitated successful liver transplantation, with most experiences being in those with less severe POPH [48, 63, 64]. The dramatic haemodynamic improvement with the 6-week addition of imatinib 400 mg daily (a tyrosine kinase inhibitor) to pre-liver transplantation *i.v.* epoprostenol and post-liver transplantation bosentan therapy, resulted in liberation of all pulmonary vasomodulation medications and normalisation of RV function 1 year post-liver transplantation. This observation suggests a possible fourth pathway of pulmonary vasomodulation effectiveness (blocking platelet-derived growth factor receptors) in treating POPH [60].

The use of beta blockers or transjugular intrahepatic portosystemic shunting (TIPS) in the POPH setting may be problematic. The former, used to prevent gastrointestinal bleeding by reducing the degree of portal hypertension, may impair needed RV function. In moderate-to-severe POPH (n=10; mean $P_{pa}$ 52 mmHg), withdrawal of beta blockers increased cardiac output by 28%, decreased PVR by 19% with no change in mean $P_{pa}$ and increased 6-minute walking distance (6MWD) by 79 m [76]. TIPS, as a treatment for uncontrollable gastrointestinal bleeding or refractory ascites, can temporarily increase mean $P_{pa}$, cardiac output and PVR. In a study of 16 cirrhotic patients without PAH, the increase in mean $P_{pa}$ was greater than that noted in cardiac output, suggesting an increase in the PVR after TIPS [77]. Such changes remained for at least 30 days post-TIPS and reflected neuro-humoral effects as opposed to increased pre-load. A significant increase in RV work was documented and the potential effect on RV function could be deleterious in patients with pre-existing POPH [78].

## Liver transplantation

To place the POPH-liver transplantation issue in perspective, there were over 6,000 liver transplants accomplished in the USA in 2011; as of mid-2012, there were approximately 16,000 patients on the waiting list in over 120 US liver transplant centres (United Network for Organ Sharing (www.unos.org) and Organ Procurement and Transplantation Network (http://optn.transplant.hrsa.gov/)). Assuming up to 8.5% of liver transplantation candidates have POPH, at any point in time there may be ~1,300 POPH-liver transplantation candidates [31]. The outcome of POPH following liver transplantation remains unpredictable despite screening, careful patient selection, higher priority for liver transplantation and advances in single and combination pulmonary vasomodulation therapies (table 4) [50, 53–56, 61, 62, 65, 66, 71,]. Current policy espoused by the American Association for the Study of Liver Disease (AASLD) calls for TTE screening to detect PH in every patient considered for lung transplantation in the USA [79]. This policy originated from documentation reported in a literature review that POPH was first

**Table 4.** Model for End stage Liver Disease (MELD) exception criteria for portopulmonary hypertension (POPH)

| |
|---|
| **Moderate-to-severe POPH diagnosis confirmed by RHC** |
| Mean $P_{pa}$ ⩾35 mmHg |
| PVR ⩾240 dyn·s·cm$^{-5}$ |
| $P_{pcw}$ ⩽15 mmHg |
| **Pulmonary vasomodulating therapy initiated; improvement documented** |
| Mean $P_{pa}$ <35 mmHg |
| PVR[#] <400 dyn·s·cm$^{-5}$ |
| Satisfactory RV function by transthoracic echocardiography |
| **MELD exception updated every 3 months** |
| Give additional MELD exception if RHC data satisfies the improvement criterion |

RHC: right heart catherterisation; $P_{pa}$: pulmonary artery pressure; PVR: pulmonary vascular resistance; $P_{pcw}$: pulmonary capillary wedge pressure; RV: right ventricular. [#]: if PVR is normal, higher mean $P_{pa}$ may be allowed and reconsidered due to physiology that is now high flow rather than flow obstruction due to the therapy.

diagnosed in the operating room in 65% of patients (n=43; 18 peer-reviewed studies), with 35% mortality in patients subsequently transplanted; pre-liver transplant mean $P_{pa}$ >35 mmHg (untreated) was associated with mortality [11]. Studies by CASTRO *et al.* [62], STARKEL *et al.* [53] and SANER *et al.* [54] reported first diagnosing POPH in the operating room after anaesthesia induction (in eras prior to current pulmonary vasomodulation therapies), noting that mild-to-moderate POPH patients (mean $P_{pa}$ <35 mmHg) do quite well without pre-liver transplantation pulmonary vasomodulation therapy intervention. The goal of screening is to identify and pre-liver transplantation treat those who have the highest risk of cardiopulmonary adversity during and after lung transplantation. Pulmonary haemodynamics in liver transplantation candidates may change over time; therefore, repetitive screening (every 12 months) is highly appropriate [32].

Effective pulmonary vasomodulation therapy has resulted in successful liver transplantation and liberation from pre-liver transplantation pulmonary vasomodulation therapy (table 3). Importantly, it is to be stressed that a key moment during the liver transplant procedure is with reperfusion when preload can increase, cytokines may be released, thrombi may migrate into the pulmonary circulation and intraoperative death follows from acute right heart failure [80].

Although supporting data are limited, liver transplantation programmes in the USA now allow a higher priority to conduct liver transplantation if pulmonary haemodynamics can be significantly improved and meet standardised MELD exception guidelines. The intention of such recent policy changes in US transplant programmes has been the hope of not only interrupting the natural history of POPH (reduce waiting list death), but also to improve post-liver transplantation survival and liberate patients from pulmonary vasomodulating therapy after successful liver transplantation if pulmonary haemodynamics have normalised (table 4). It is important to emphasise that POPH by itself cannot be considered as the sole indication for liver transplantation; the severity of liver disease/portal hypertension is the primary reason for transplant consideration.

Although the role of liver transplantation in the setting of POPH is evolving with experience, the recognition that severe POPH (measured haemodynamically and qualitatively by echocardiography) can resolve post-liver transplantation with aggressive pre-liver transplantation pulmonary vasomodulation therapy is quite remarkable. The frequency and prognosis of those with moderate-to-severe POPH who do not resolve after liver transplantation is unknown. The limited literature and recent Mayo Clinic experience suggest that more than 50% of pulmonary vasomodulation-treated POPH can be liberated from pulmonary vasomodulation medication post-liver transplantation [37, 46, 58]. However, the risk of liver transplant in the setting of POPH remains unpredictable, even if pulmonary haemodynamics are improved [31, 46, 51]. Although preliminary observations are encouraging, the normalisation of pulmonary haemodynamics post-liver transplantation does not necessarily equate to pulmonary vascular pathology resolution or long-term stability. Finally, it should be noted that clinically significant PAH can develop *de novo* following liver transplant (*i.e.* normal pulmonary haemodynamics are noted at the time of liver transplantation) for reasons that are clearly not understood [68].

### *Statement of Interest*

M.J. Krowka has been a member of the Gilead Advisory Board (makers of ambrisentan) for pulmonary artery hypertension matters. M.J. Krowka wrote a paper describing the safety and efficacy of using ambrisentan in portopulmonary hypertension but no specific recommendations that would bias the reader to use that medication over any other medication were made. M.J. Krowka has received an honorarium for the period 2011–2012 of ~$5,000.

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# Chapter 6

# Managing pulmonary hypertension in patients with congenital heart disease

*Damien Bonnet and Marilyne Lévy*

**SUMMARY: Pulmonary hypertension (PH) associated with congenital heart disease (CHD) is a heterogeneous condition that ranges from systolic hypertension with massive pulmonary blood flow in infantile left-to-right shunts, to Eisenmenger's syndrome. The rapid progress that has been made in this field is essentially due to the availability of new pulmonary arterial hypertension (PAH) drugs, which can be used in patients only previously managed with supportive therapy. The successes and limitations of the new therapies have allowed further definition of the subtypes of PH associated with CHD. The emergence of a system of classification for the condition indicates the complexity of a problem that is highly significant in terms of morbidity and mortality. Manipulating the variety of clinical forms of PAH and PAH associated with CHD has increased knowledge about the pathophysiology of these conditions. This new information will certainly improve patient management and outcome.**

**KEYWORDS: Congenital heart disease, Eisenmenger's syndrome, left-to-right shunt**

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Pulmonary hypertension (PH) in congenital heart disease (CHD) is a broad topic. The heterogeneity of PH in patients with CHD has different levels, and these will be discussed in this chapter (fig. 1). Increased pulmonary artery pressure ($P_{pa}$) is a common characteristic of patients with large, non-restrictive, post-tricuspid septal defects without right outflow tract obstruction. In these systemic-to-pulmonary shunts, PH is usually concomitantly diagnosed early in life with CHD, and repair of the defect leads to normalisation of pulmonary pressure when performed before the development of pulmonary vascular disease. The first level of heterogeneity is therefore the age of the patient at the time of diagnosis. Age at diagnosis strongly influences the management of PH, as the condition differs greatly in infants and adults with the same cardiac lesion [1]. The second level of heterogeneity is the type of defect, as the development of pulmonary vascular disease and pulmonary arterial hypertension (PAH) occur at different rates according to the type of defect [2]. Furthermore, depending on associated factors such as prematurity, chromosomal anomalies, genetic susceptibility and unknown factors, the onset and

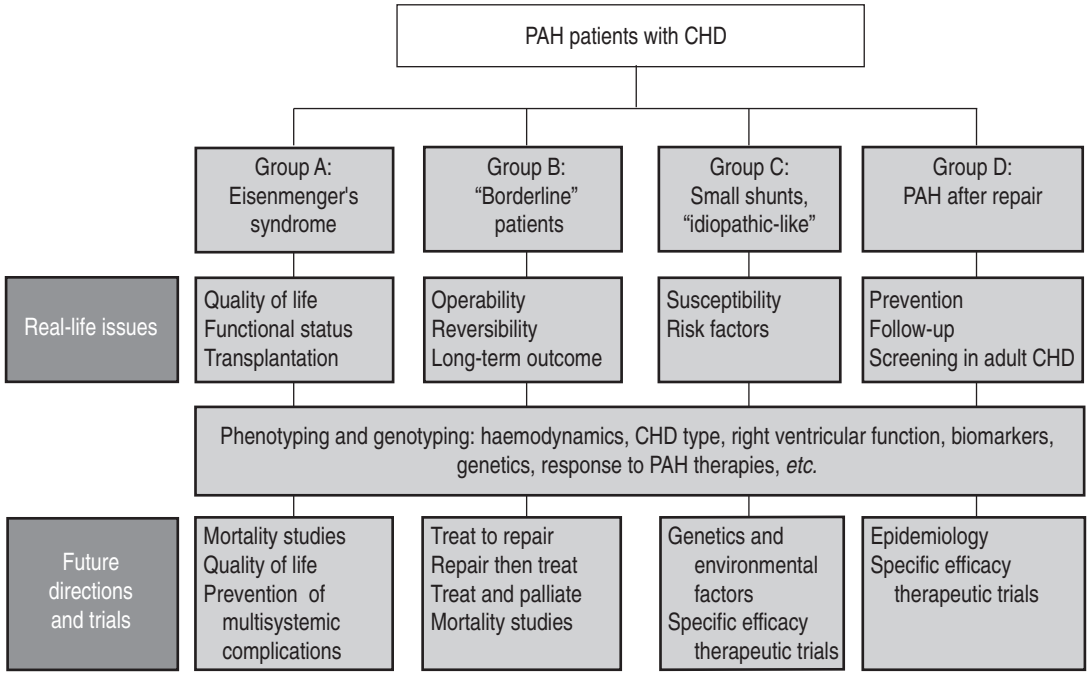


**Figure 1.** Problems and future directions in subgroups of pulmonary arterial hypertension (PAH) patients with congenital heart disease (CHD).



evolution profile of pulmonary vascular disease in one anatomical type of CHD may vary between patients of the same age [3]. PH and PAH associated with CHD have most often been described and studied in left-to-right shunts; however, there are unusual cases in the paediatric population in which PAH is apparently not causally related to CHD, and is not "out of proportion" because there is no left-to-right shunt or because PAH occurs too early in life [4]. Similarly, whilst pulmonary vascular abnormalities are generally localised on the arterial side and post-capillary PH should be the rule in patients with left heart congenital obstructive defects, it is not uncommon to observe a severe elevation of pulmonary vascular resistance (PVR) in these patients [5]. Finally, chronic pulmonary vascular disease is increasingly seen in adult patients with repaired congenital cardiac disease and is an important cause of morbidity and mortality [6].

Pulmonary vascular disease associated with CHD represents one of the most preventable forms of PAH. However, the wide range of physiologies of PH associated with CHD, ranging from classic large ventricular septal defects (VSD) to the intricacies of left heart PH and a variety of Eisenmenger's syndrome phenotypes, means designing trials in such patients is complex and proposing meaningful practical advice or treatment algorithms remains a challenge.

In this chapter, we will summarise the standard approaches to management of PH in CHD and discuss the challenging issues in this field.

## Classifications of PH in CHD

The Dana Point clinical classification of PH proposes the identification of various subgroups, which have similar presentation and pathophysiological mechanisms [1, 7]. In this classification, PAH associated with left-to-right shunt has been classified into four subgroups, considering the type of cardiac diagnosis, the prognosis and evolution of pulmonary vascular disease, and the circulatory physiology (table 1). This classification clearly does not embrace all clinical forms of PH and PAH associated with CHD. Nevertheless, it has the advantage of allowing simple classification of PAH patients, according to practical information that can be widely used.

**Table 1.** Clinical classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (PAH)

**Group A: Eisenmenger's syndrome**
Eisenmenger's syndrome includes all systemic-to-pulmonary shunts caused by large defects, leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis and multiple organ involvement are present.

**Group B: PAH associated with systemic-to-pulmonary shunts – ''borderline'' PAH with CHD**
In patients with moderate-to-large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

**Group C: PAH with small defects – ''idiopathic-like'' PAH with CHD**
In cases with small defects (usually VSD <1 cm and atrial septal defects <2 cm of the effective diameter assessed by echocardiography), the clinical picture is very similar to IPAH.

**Group D: PAH after corrective cardiac surgery**
In these cases, CHD has been corrected, but PAH is either still present immediately after surgery or has recurred several months or years after surgery, in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela of previous surgery.

PVR: pulmonary vascular resistance; CHD: congenital heart disease; VSD: ventricular septal defect; IPAH: idiopathic PAH.

This approach can be used in the vast majority of adult patients with PAH complicating with left-to-right shunts, and clinical trials can be designed using this type of classification. The four categories of PAH patients with CHD have also allowed the consideration of unresolved questions in the field. The management of patients with Eisenmenger's syndrome (group A) has changed in recent years owing to a better understanding of the whole figure of the disease and the availability of new medical options. For group B, the recurring question ''can the shunt be closed?'' is largely unanswered. Group C includes patients who have PAH that resembles idiopathic PAH (IPAH), which should perhaps be managed as IPAH in children and in adults. The last category is chronic post-operative PAH after repair, which also resembles IPAH but appears to have the worst prognosis among the different groups of PAH patients with CHD. It is noteworthy that recent literature uses a variety of names for the different categories of PAH patients with CHD, which may be confusing for non-expert readers and will certainly limit the possibility of analysis and comparison of registries and clinical trials [3, 4, 8]. A consensus approach to the classification of paediatric pulmonary vascular disease has recently been proposed to attempt to solve the complexities of paediatric PH [8].

In countries with structured referral patterns, the prevalence of PAH associated with CHD is decreasing because repair is proposed early in life; however, in other parts of the world, it remains a major health problem that could be prevented by improved screening and surgical treatment in children. If PH directly caused by CHD in children is excluded, the questions are limited and could be derived from the Dana Point classification. The first question for patients in group B relates to the reversibility of pulmonary vascular disease. The second question for patients in group D relates to the organisation of follow-up after CHD repair to for allow early PAH treatment. The third question regards the management of Eisenmenger's syndrome patients (group A), with the aim of improving survival and quality of life. Finally, for patients of group C, management should probably be identical to IPAH; this group of patients is certainly exciting due to the identification of factors that accelerate the evolution of pulmonary vascular disease.

## Reversibility of pulmonary vascular disease in CHD

Successful corrective surgery for CHD has become widely available and repair of defects that are associated with increased pulmonary blood flow is usually performed in very early infancy. These procedures aim to prevent the development of PAH. In some individuals with left-to-right shunt, such defects may pass undetected until childhood or even adulthood, and are diagnosed late when pulmonary vascular lesions develop. Therefore, there is a need for guidance concerning complete

surgical repair or palliative surgery in CHD patients who develop PAH as a result of their haemodynamic condition.

While the underlying pathophysiological changes that occur in the pulmonary vasculature are similar, the type of heart defect, the circulatory pathophysiology and the evolution and progression of PAH influence patient management.

It is worth noting that patients with moderate-to-large defects can have PAH but not necessarily irreversible pulmonary vascular disease in terms of a permanently and extensively altered pulmonary vascular bed [9, 10]. Undeniably, the decision to operate is the most difficult in patients who have moderate increases in PVR, as the extent of the pulmonary vascular lesions is unknown and there is no guarantee of long-term success [11]. Very careful assessment is required to gauge the level of risk of irreversible PAH after surgery. In the absence of an evidence-based treatment algorithm, such patients are currently managed on a case-by-case basis, according to an almost arbitrary decision made by the physician.

## Assessing operability in borderline PAH patients with CHD

The tools that are available to assess the operability of PAH patients with CHD comprise of clinical examinations and haemodynamic measurements. Clinical status and echocardiography are not reliable tools for assessing the operability of borderline patients. Right heart catheterisation (RHC) is now mandatory for ambiguous patients. The thresholds used to predict which patients will have a positive or negative surgical outcome are still empirical.

It has recently been proposed that PVR, the ratio of PVR to systemic vascular resistance and the way these values change during acute vasodilator challenge should be used to assess operability (table 2) [12]. In a thorough review of the literature, GIGLIA and HUMPL [13] reported a consensus statement that provides precise values of haemodynamic measurements of pulmonary vascular disease to determine the level of risk of death or persistent elevated PVR following biventricular repair. While these studies are in agreement, it is still unclear which pre-operative pulmonary haemodynamic parameters correlate best with outcomes. Some of the patients that fall within the ranges deemed appropriate for determining a good long-term outcome may still present with persistent post-operative PAH. In a series of patients with moderately elevated PVR (mean $\pm$ SD pre-operative PVR of 7.63 $\pm$ 1.8 Wood units), it has been shown that one-fifth either died or had persistent severe PAH following corrective surgery for VSD [14]. For these reasons, more accurate and preferably less invasive evaluation tools are required, particularly in patients whose operability is uncertain due to their haemodynamic profile.

Lung biopsy is not currently used to evaluate the histopathological changes in the pulmonary vasculature as the reliability of the results is not considered sufficient to justify the invasive nature of the procedure and the risks involved in obtaining a lung tissue sample [15]. Circulating endothelial cells, a novel marker of endothelial damage, have recently emerged as a putative

**Table 2.** Suggested haemodynamic criteria to assess the operability of pulmonary hypertension (PH) patients with congenital heart disease (CHD)

| |
|---|
| A baseline PVR index <6 Wood units·m$^2$ associated with a PVR/SVR ratio of <0.3 without a vasoreactivity test may be considered indicative of a favourable outcome following operations resulting in biventricular circulation |
| Acute vasodilator challenge using oxygen and NO has been strongly encouraged if the baseline PVR index is 6–9 Wood units·m$^2$ in the presence of a PVR/SVR ratio of ~0.3–0.5. Although there is no absolute consensus, operability with a favourable outcome is considered likely if all the following criteria are met: |
| A decrease of 20% in the PVR index |
| A decrease of ~20% in the PVR/SVR ratio |
| A final PVR index <6 Wood units·m$^2$ |
| A final PVR/SVR ratio of <0.3 |

PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; NO: nitric oxide. Data from [12].

predictor of reversibility of PAH associated with CHD [11, 16]. In this by SMADJA *et al.* [16], patients who had irreversible PAH were shown to have increased circulating endothelial cell counts compared with those who had reversible PAH, while the haemodynamic data of both groups was comparable. In contrast, other biomarkers of endothelial activation, regeneration and injury have not been able to discriminate between reversible and irreversible PAH following surgery [17].

Nowadays, in order to decide upon the most appropriate therapeutic strategy in "borderline" patients (including their operability), we have to take the full picture into consideration, *i.e.* age, clinical history, physical examination, and the results of noninvasive and invasive diagnostic procedures.

## Therapeutic management of borderline PAH patients with CHD

Having defined which patients are at a high risk of post-operative progression of the disease following CHD repair, the challenge is to determine strategies that could lead to beneficial "de-remodelling" in cases in which lesions of the pulmonary vascular bed are not fixed or irreversible, thus allowing surgical repair. It has been reported that after shunt closure, PAH patients with CHD showed similar survival to IPAH patients, with a 1-, 3- and 5-year survival of 93%, 68% and 51% respectively [3, 18]. Closing the shunt when reversibility of pulmonary vascular disease is unlikely is a crucial mistake, as early post-operative outcome might be stormy and mid-term mortality is high.

An alternative for high-risk patients is pulmonary artery banding (only in post-tricuspid intracardiac shunts), although there is presently no evidence to support a recommendation for this treatment [19]. The hypothesis is that removal of the haemodynamic stimuli on the pulmonary vessels would be followed by reversal of pulmonary vascular disease [20]. This reversibility after haemodynamic unloading was demonstrated by WAGENVOORT *et al.* [21], who showed reversal of pulmonary vasculopathy in CHD patients after pulmonary artery banding. Haemodynamic unloading is also associated with a decreased number of proliferating cells and a decrease in medial thickness in experimental PH [20, 21]. No controlled human studies have demonstrated the efficacy of pulmonary artery banding in a group of CHD patients evaluated precisely for their haemodynamics. Perioperative management of pulmonary artery banding may be difficult because of severely reduced pulmonary blood flow, right ventricular (RV) dysfunction and cyanosis. The use of telemetrically adjustable banding may be advantageous in such cases [22]. A partial closure may be more difficult in pre-tricuspid shunts (atrial septal defects) and arterial shunts (patent arterial duct). Various percutaneously implantable devices have been designed for the purpose but are not currently used [23].

Experimental studies have indicated that prostanoids, endothelin receptor antagonists (ERAs) and phosphodiesterase type-5 inhibitors (PDE-5 I) exert antiproliferative effects on vascular endothelial and smooth muscle cells [24, 25]. These drugs have been approved for use in PAH and have been extensively tested in IPAH; there is also strong evidence that some of them are effective in treating PAH patients with CHD [26–29]. The subsequent hypothesis for borderline PAH patients with CHD is the reduction of PVR in patients without extensive vascular lesions, in order to allow operability. Regarding surgical procedures (repair or palliation), patient selection is the key problem to potential trials that are still lacking. In addition, although it is rapidly effective on PVR, the use of a vasodilator can lead to an increase pulmonary blood flow that will re-establish the propensity towards lesion occurrence. The combination of a palliative surgical procedure to calibrate pulmonary blood flow and the use of targeted PAH therapy may be a good option but large trials will obviously never be performed. Another unsolved question is the type of PAH drug that should be used. As the aim is to reverse pulmonary vascular disease, the most logical approach would be to combine the drugs acting on the three key pathways involved in the pathophysiology of PH, *i.e.* the endothelin pathway, the prostacyclin ($PGI_2$) pathway and the nitric oxide (NO) pathway. Furthermore, using these drugs as an upfront combination rather than sequentially, as is currently done in PAH treatment, is a more rational way of generating rapid action on pulmonary

vasodilatation, smooth muscle proliferation and hypertrophy of the pulmonary arterial vessels. A variety of case reports show success with pre-treatment prior to operability, but we do not know how many cases have failed and have not been reported [30–34].

In a study by HUANG *et al.* [35], PAH patients with CHD who were previously considered inoperable for surgical correction were selected and submitted to a ''treat and repair'' programme, during which lung biopsies were taken. Patients underwent surgery when clinical assessment was in favour of increased pulmonary blood flow. More than 80% of the patients who were ''repaired'' had shown histological changes considered suitable for surgery (grades I and II of the Heath and Edwards histology classification system of hypertensive pulmonary vascular disease); conversely, 59% had severe post-operative PAH. ''Repair and treat'' is the other option. In a short series of three patients with atrial septal defects and PVR ranging 6–12 Wood units, who were treated with $PGI_2$, after closure of the shunt, PVR was shown to remain below pre-operative levels after a mean follow-up of 3.4 years [36]. A single ambiguous case of a 35-year-old female with patent arterial duct and PAH showed that bosentan improved clinical status after closure of the duct; however, no haemodynamic data are available [37].

Currently, no precise algorithm to treat these patients is available. It is interesting to note that in attempting to solve this issue, important progress has been made in the evaluation of these patients and different phenotypes of PAH with CHD have begun to emerge [3, 11]. It is hoped that the information obtained from large registries and/or dedicated therapeutic trials will improve our knowledge in this field and will clarify whether borderline patients are best managed with surgery, pharmacological therapy or a combination of both.

## Follow-up and screening for post-operative PAH patients with CHD

The type of CHD and the age of the patient are the two most important factors in determining the onset of pulmonary vascular disease and subsequent PAH. Pulmonary vascular disease develops very early in aortic origin of one pulmonary artery, while in atrial septal defect, PAH is observed later in life, after 20 years of age. These natural histories determine the date of repair. However, the natural course of PAH after repair of CHD may vary between individuals; it may take weeks or even months for $P_{pa}$ to return to normal. For this reason, in ongoing clinical trials of post-operative PAH with CHD, patient selection begins 6 months to 1 year after surgery. Similarly, it is of utmost importance that children whose pulmonary haemodynamics fail to normalise undergo close follow-up, as pulmonary vascular disease may worsen after an asymptomatic period [38, 39]. Indeed, closing a shunt in a borderline patient can dramatically improve symptoms. This is very interesting in elderly patients with atrial septal defects, moderately elevated pulmonary blood flow, PAH with high PVR and left ventricle (LV) diastolic dysfunction, as suppression of the shunt will reduce pulmonary wedge pressure and dyspnoea, and the evolution of pulmonary vascular disease will hopefully remain slow. The same approach in young patients will aggravate their condition, as previously discussed [3, 18]. In adult CHD registries, it has been shown that the prevalence of PAH increases with age both in patients with open and with closed shunts [6]. This suggests that even in simple CHD conditions, such as atrial septal defects, patent arterial duct or VSD, long-term follow-up of $P_{pa}$ is mandatory, even if regular follow-up during childhood has shown normal pulmonary pressure. Recently, it was reported that 25% of adult PAH patients with CHD included in the French PAH registry had repaired defects (X. Jaïs, Université Paris Sud, Paris, France; personal communication). The delay between the repair and diagnosis of PAH was less than 1 year in 10% of patients and as long as 20 years in approximately half of the population. This is due to the high proportion of patients who were lost to follow-up because they were asymptomatic and had been told that follow-up was not necessary. This incorrect attitude should be modified, and regular follow-up of adults with CHD should be organised in expert centres, in order to screen them for elevated $P_{pa}$ as well as for other common adult CHD complications.

Treatment of post-operative PAH with PAH drugs has been reported to be beneficial. This specific treatment should be proposed after careful and thorough evaluation of PH causes that can be remedied, such as upper airway compression, residual shunts, valve or LV dysfunction, pulmonary vein stenosis or proximal pulmonary artery distortion. Improvement of symptoms and an increase in 6-minute walking distance (6MWD) has been demonstrated with sildenafil [40, 41], bosentan [18], inhaled iloprost [42] and intravenous prostacyclin in this group [29]. The point at which treatment with a specific drug should be terminated is as yet unclear, and these patients should potentially be treated throughout their life, as they behave like IPAH. There is no information on the efficacy of these treatments on outcomes.

## Improving Eisenmenger's syndrome prognosis

Medical management is improving in patients who are deemed inoperable according to the commonly used criteria, particularly in those with Eisenmenger's syndrome. Indeed, knowledge of the complex consequences of chronic cyanosis, as well as the physiology of cardiac and respiratory function in these patients, has been a source of progress in the management of this population. A variety of questions have emerged: what is the best time to initiate pharmacological treatment? Should all patients be treated? And which outcome measures should be used to monitor their response? Supportive measures are a major part of the management of patients with Eisenmenger's syndrome. Precautions related to pregnancy, extracardiac surgery and anaesthetic management have been expansively described [10]. More recently, the importance of iron-deficiency treatment has been highlighted [43], as an improvement in haemoglobin levels may be beneficial to exercise capacity and quality of life.

Functional evaluation of Eisenmenger's syndrome patients has shown that they have the highest rates of functional impairment and mortality among adult PAH patients with CHD. In the Euro Heart survey, 20.6% of Eisenmenger's syndrome patients died during a 5-year follow-up period [6].

The evidence base for the use of PAH-specific drugs is still in its early stages. The BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) trial, which compared bosentan with placebo in Eisenmenger's syndrome patients in functional class III, showed significant reductions in PVR and mean $P_{pa}$, as well as an increase in 6MWD [26]. This was confirmed in the open-label extension [27], and improvement was shown to be independent of the underlying cardiac defect [28]. More importantly, in BREATHE-5 PVR deteriorated during the study period in patients who received placebo, highlighting the fact that Eisenmenger's syndrome is an evolving process and raising once again the question of whether to treat these patients at the early phase of disease in an attempt to slow the extent of pulmonary vascular disease. To date, there is no clear information on the early treatment of Eisenmenger's syndrome patients, as only a very small number were included in in a recent randomised controlled trial that included mildly symptomatic patients [44]. In a small randomised controlled trial, sildenafil has been shown to improve 6MWD, haemodynamic measurements and functional status in 10 patients with Eisenmenger's syndrome [45]; prospective data support these findings [46]. A larger randomised trial with 7% Eisenmenger's syndrome patients showed a significant benefit after 19 months [47]. Sildenafil is often used as an add-on therapy to bosentan, and this current attitude has been supported, although not proven, in a recently published clinical trial in patients with Eisenmenger's syndrome [46]. Tadalafil has recently emerged as an alternative treatment, demonstrating a significant increase in 6MWD, haemodynamics and oxygen saturation in PAH patients with CHD [48]. Combination therapy in Eisenmenger's syndrome patients (sildenafil and bosentan) resulted in a significant improvement in clinical status, arterial oxygen saturation ($S_{a,O_2}$) measured by pulse oximetry ($S_{p,O_2}$) [2], exercise tolerance and haemodynamics [49]. Data on the use of prostanoids in PAH patients with CHD are scarce. The administration of *i.v.* epoprostenol improves 6MWD, oxygen and haemodynamics in PAH patients with CHD. Management of central lines is the main problem with *i.v.* prostanoids, as the risk of endocarditis, thrombosis and paradoxical emboli limits their use. Alternatively, subcutaneous treprostinil can be used but no data are available.

A recent study of 229 patients with Eisenmenger's syndrome, who were treated between 1999 and 2008 at the Royal Brompton Hospital (London, UK), summarises the role of PAH-specific therapies in these patients [50]. 52 of the 229 patients enrolled in the study died during follow-up (median 4 years) and the vast majority of deaths occurred in the patients who did not receive PAH-specific therapy. This observational and retrospective study does not provide proof of the efficacy of PAH-specific drugs on mortality in Eisenmenger's syndrome, but it does suggest that modern management is certainly important in this improvement.

Finally, the functional evaluation of patients with Eisenmenger's syndrome is a key issue, as it will be very difficult to prove that PAH drugs are effective with a hard end-point, such as mortality, as the survival period is lengthy [51]. The implementation of a more precise evaluation of functional status, using the most pertinent parameters of exercise testing and a potentially holistic approach, including clinical status, RV function parameters, biomarkers, haemodynamic measurements and response to pharmacological therapies, is an interesting area of future consideration [52].

Transplantation is the only potentially curative option in Eisenmenger's syndrome. The main consideration is the determination of the optimal transplantation timing, as the 10-year survival rate is only 30–40% for a transplanted heart/lung; this is much lower than expected in Eisenmenger's syndrome. The criteria for transplantation therefore remain unclear.

## Idiopathic-like PAH in CHD

This group of patients (group C of the PAH patients with CHD) is surprising. These patients have a small cardiac defect that is not considered to be responsible for PAH because the shunt is too small to produce high pulmonary blood flow and the subsequent effects on pulmonary vasculature. This is perhaps the most mysterious group of PAH patients with CHD, and progress certainly needs to be made to further characterise these patients. The fortuitous association of IPAH and a small atrial septal defect may occur, but statistically, this association should be exceptional. The role of a second factor, namely acceleration of pulmonary vascular disease in patients with PAH gene mutation and a small shunt, has not been proven as mutation in PAH genes is exceptionally found in PAH patients with CHD [53]. In addition, idiopathic-like profiles can also be seen in patients with large shunts and do not clearly belong to this group. These patients have been named "accelerated Eisenmenger" in the Dutch registry [3]. Finally, some PAH patients with this kind of CHD do not have left-to-right shunt; for example, patients with PAH complicating transposition of the great arteries [54, 55]. Many hypotheses have been formed to explain these different forms of PAH but no clear explanation has as yet been found. Management is identical to IPAH but the evolution might be more severe.

## Post-capillary PH in CHD

PH in patients with left-heart CHD is a largely unresolved issue. The most striking example is pulmonary vein stenosis, but this complex situation may also be observed in neonates with diminutive left ventricles with or without left outflow tract obstruction. In these patients, it is not uncommon to observe a severe rise in PVR, with elevated pulmonary wedge pressure but "out of proportion" PH. The mechanism for this pre-capillary PH is unknown. These patients, and particularly those with pulmonary vein stenosis, have a very guarded prognosis and long-term survival is rare [56].

## Future directions

Establishing a common practice to assess the haemodynamic phenotype of PAH patients with CHD is essential for the inclusion of patients in trials. Sharing end-points that can reasonably be reached within a realistic timeframe is also a key point for the future. In addition, extending the use of available drugs in IPAH to PAH patients with CHD in randomised controlled trials will

certainly be important for the better management of the increasing population of affected patients. Modulating PVR in complex CHD will become a common practice as a high number of patients will survive until adulthood, and these patients will be more complex to diagnose, treat (because of comorbidities such as cardiac failure and arrhythmias) and evaluate (because of associated anomalies such as pacemakers, valvar regurgitation and respiratory problems).

## Conclusion

PAH in CHD has become an important problem in centres dealing with these patients. While Eisenmenger's syndrome was considered to be the end of the story, it should now be considered a medically treatable disease. The burning issue remains the strategy to best treat borderline patients and allow a favourable outcome in the long term. An objective of the near future should be the delineation of the different phenotypes of this group of patients, as well as those of the idiopathic-like group.

### *Statement of Interest*

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# Chapter 7

# Pulmonary arterial hypertension in patients with HIV infection

*Harrison W. Farber*

**SUMMARY: With the advent of highly active antiretroviral therapy (HAART), there have been significant reductions in infectious complications with HIV; however, the prevalence of HIV-associated pulmonary arterial hypertension (HIV-PAH) has not changed. HIV-PAH can occur at any point during the disease and no definitive association with CD4 count or viral load has been observed. The aetiology and pathogenesis of HIV-PAH remains poorly characterised, although a number of observations in a simian immunodeficiency virus (SIV) model and *in vitro* studies support a pathogenic role for HIV proteins. Although there are no randomised controlled trials of treatment for HIV-PAH, therapies are currently similar to those employed for other forms of PAH; however, there are potential interactions between PAH medications and antiretrovirals and potential effects on hepatic function. Nonetheless, limited series of patients treated with epoprostenol or bosentan have demonstrated acute and chronic benefits of pulmonary vasodilators in patients. As HIV-infected patients are living longer, HIV-PAH is likely to become a more frequent complication, despite the increased access to HAART.**

**KEYWORDS: AIDS, highly active antiretroviral therapy, HIV infection, pulmonary arterial hypertension, pulmonary hypertension, pulmonary vasodilators**

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Among the 30–40 million people infected with HIV, the primary pulmonary complications for adults are infections. However, HIV-infected persons who receive highly active antiretroviral therapy (HAART), the spectrum of pulmonary pathology is changing: there has been a decrease in the incidence of opportunistic infections and an increase in non-infectious complications [1]. HIV-associated pulmonary arterial hypertension (HIV-PAH) is among these non-infectious complications.

First described in 1987 by KIM and FACTOR [2], HIV-PAH is histologically similar to idiopathic pulmonary arterial hypertension (IPAH), although differences in disease incidence and rate of progression suggest different causative mechanisms [2–4]. In 1991, SPEICH *et al.* [5] reported a

prevalence of 0.5% for HIV-PAH in their cohort of 1,200 patients. As these patients were all characterised in 1990, it was speculated that, with the advent of HAART and the resulting improvement in viral control, there would be a change in prevalence. However, a report by SITBON *et al.* [6] in 2008 suggested that this was not the case. In a large, multicentre cohort of 7,648 HIV-infected patients, who were studied between 2004 and 2005, the prevalence of HIV-PAH was 0.46%, essentially unchanged from that found in 1990 [6]. This unchanged prevalence in HIV-PAH is in stark contrast to another pulmonary complication of HIV infection, *Pneumocystis* pneumonia, in which the total number of cases declined five-fold between 1995 and 2003 [7]. However, data from the extension of the Swiss HIV cohort study [8] suggests that although the prevalence of HIV-PAH may not have changed, the incidence of newly diagnosed cases may be declining. This may be due to differences in population mix as a result of changes in modes of transmission or possibly higher CD4 cell counts and a decrease in immune activation because of more efficient antiretrovirals.

The stable prevalence of HIV-PAH does suggest: 1) the prevalence of PAH among HIV-infected patients is, and will remain, much greater than IPAH (six- to 12-fold greater); 2) Since 30–40 million people in the world are infected with HIV and survival time is much longer, the number of HIV-PAH cases identified is certain to increase; and 3) Since the prevalence of PAH in HIV-infected people is essentially unchanged in spite of a reduced viral load, the pathogenesis of HIV-PAH is only partly dependent on the degree of HIV viraemia. The clinical implication of these observations is that current and investigative therapies used in PAH should significantly reduce the symptoms and improve the quality of life in HIV-PAH patients. The major limiting factor for the use of any PAH-modulating medication is the complicated pharmacokinetics related to concurrent antiretroviral used and the higher prevalence of hepatic impairment among HIV-infected patients [9]. Despite these limitations, it seems reasonable that, as is the case with other types of PAH, early intervention has the potential for significantly delaying disease progression.

## Pathology of HIV-PAH

HIV-PAH is included with IPAH in the World Health Organization (WHO) group 1 classification because the histology of pulmonary arterial lesions is indistinguishable from other entities in this group [10]. The original 1987 observation identified pre-capillary pulmonary arteries with endothelial cell clusters filling the lumen in a 40-year-old HIV-infected male who died of *Pneumocystis* pneumonia [2]. This initial observation was subsequently confirmed in reports of other HIV-infected patients with PAH [5, 11–15]. Interestingly, in a retrospective report of 131 published HIV-PAH cases, the majority (78%) of patients had plexiform lesions; however, other histologies were observed, including thrombotic pulmonary arteriopathy, pulmonary medial hypertrophy with intimal fibrosis, and pulmonary veno-occlusive disease (PVOD) [16]. More recently, there have been HIV-PAH cases with evidence of perivascular inflammatory cells suggesting yet another potential mechanism for the development of HIV-PAH [17, 18].

## Pathobiology of HIV-PAH

The aetiology of HIV-PAH is likely to be multifactorial, resulting from a combination of viral and host factors as shown in figure 1. A number of putative mechanisms by which an HIV infection might directly cause or elicit a cellular environment that would lead to the development of the hallmark plexogenic arteriopathy and haemodynamic pathology have been proposed. These presumed mechanisms of disease development relate directly to the virus, to the host's response to HIV-infection and/or to the consequent infections or diseases that resulted from HIV-induced immune deficiency.

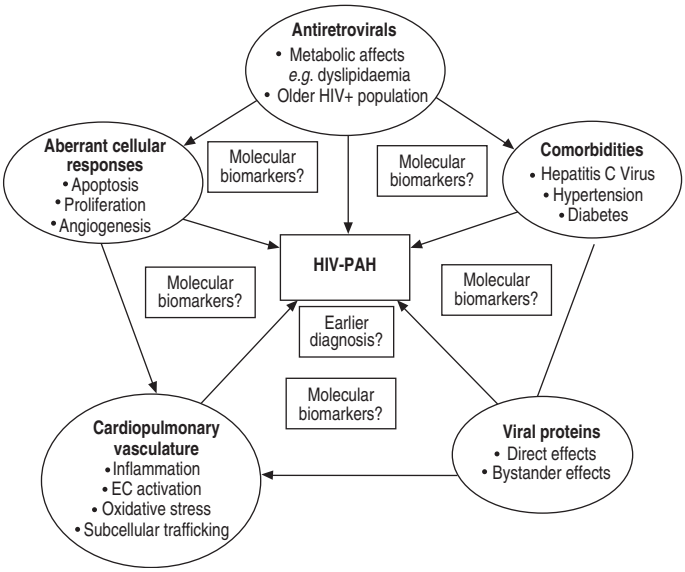


**Figure 1.** Potential pathways and interactions in the development of HIV-associated pulmonary arterial hypertension (HIV-PAH). EC: endothelial cell. Reproduced and modified from [19] with permission from the publisher.

## Direct effects of HIV

The proposed mechanisms that invoke a direct effect of HIV infection have, in general, focused on viral proteins being mediators. These HIV proteins are generated during viral replication and are known to be bioactive as well as being integral to HIV-induced pathogenesis [20–25]. The HIV proteins that have been studied for their potential to contribute to the development of HIV-PAH include glycoprotein (gp)120, trans-activator of transcription (Tat), negative-regulator factor (Nef) and envelope protein (Env).

Tat is an HIV protein that, in addition to being required for viral replication, interacts with a number of cytoplasmic and nuclear proteins. It mediates HIV pathogenesis and can cross cell membranes [25, 26]. Thus, cells that are not infected with HIV, often referred to as ''bystander'' cells, can be affected. Bone morphogenetic protein receptor type II (BMPR II) is a member of the transforming growth factor (TGF)-β superfamily receptor that transduces extracellular signals through the kinases on their intracytoplasmic tail. Heritable pulmonary arterial hypertension (HPAH) is indistinguishable pathologically from IPAH and HIV-PAH. Mutations of the *BMPR2* gene are associated with increased risk of HPAH in many, but not all, individuals in these families, suggesting that compromised BMPR II signalling can contribute to the development of PAH [27]. *In vitro* studies, which used the monocyte cell line U937, demonstrate that exposure to HIV Tat protein results in decreased *BMPR2* promoter activity and transcript copy number. Thus, HIV infection and the resulting exposure to Tat may contribute to the development of PAH by compromising BMPR II signalling in a similar manner as HPAH [28]. However, small studies have not found *BMPR2* mutations in patients with HIV-PAH. Larger population studies may be necessary to address this issue completely, or, more likely, other mechanisms are more important in the majority of individuals with HIV-PAH.

Another HIV protein, gp120, which: mediates viral pathogenesis; recruits T-cells and monocytes; impairs dendritic cell maturation and antigen-presenting capacity; and induces the secretion of a number of cytokines, including endothelin-1 (ET-1). In patients with PAH, serum and pulmonary parenchymal ET-1 levels are markedly elevated; as such, endothelin receptor antagonists (ERAs) have been used clinically to mitigate the pathology of PAH. ET-1 has potent smooth muscle proliferative and vasoconstrictive effects, as well as antiproliferative and vasodilatory effects, *via* nitric oxide (NO) and prostacyclin, depending on with which of its two G-protein coupled receptors, $ET_A$ or $ET_B$, it binds. ET-1 is produced primarily by endothelial cells but is also secreted by human macrophages [29]. Human monocytes exposed to gp120 for 24 h secrete higher amounts of ET-1. To assess the relevance of this observation to human disease, the same investigators compared monocytes isolated from HIV-infected patients at various stages of disease with healthy HIV-negative donors by real time (RT)-PCR. In eight of the 10 HIV-infected individuals, an ET-1 PCR product was clearly visible, whereas it was undetectable in the HIV-negative controls. Monocytes from other inflammatory or virus-mediated diseases were also studied as disease controls; however, none were found to have identifiable ET-1 PCR products. Finally, the investigators compared immunohistochemically stained macrophages in brain tissue

from HIV-infected patients and encephalopathy with HIV-uninfected controls. Again strong staining for ET-1 in CD68+ cells was found, consistent with brain microglia [29]. The fact that interruption of ET-1 signalling can mitigate PAH and because ET-1 is elevated in the presence of gp120 and *in vivo* HIV-infection suggest a role for gp120 in HIV-PAH. However, these studies only demonstrate association. Further studies of this HIV protein are needed to clarify its role in the pathogenesis of HIV-PAH.

The HIV proteins Nef and Env are two additional proteins that have recently been implicated in the pathogenesis of HIV-PAH. In the simian immunodeficiency virus (SIV)-infected nonhuman primates, HIV proteins can be studied by inserting the gene sequence for a specific HIV protein in place of the analogous SIV gene. Rhesus monkeys infected with simian-human immunodeficiency virus (SHIV)-*nef* develop a rapidly progressive immunodeficiency that replicates much of the pathology of HIV infection in humans, with most of the monkeys dying within 1 year [30]. In the lungs of five out of six rhesus monkeys, that had been infected with SHIV-*nef* chimaeric viruses, there was evidence of vascular remodelling with endothelial cell proliferation, compared with lungs of monkeys infected with SIV, in which no HIV Nef was present [31]. These lesions stained positive for factor VIII and muscle-specific actin. In contrast, in the SIV-infected monkeys, there was no evidence of abnormal pulmonary artery histology, suggesting that HIV Nef was associated with the vascular remodelling found in the SHIV-*nef* infected monkeys. However, whether these lesions equate to haemodynamic evidence for PAH it is not clear. MARECKI *et al.* [31] then examined lung tissue from two patients with HIV-PAH for the presence of Nef protein. In both the HIV-PAH patients and the SHIV-*nef* infected monkeys, the pulmonary artery lesions demonstrated the presence of Nef [31]. Although this provides some supportive evidence that Nef may contribute to HIV-PAH pathology, examination of lung tissue from HIV-infected patients without PAH was not performed and it is an important necessary control to bolster this hypothesis. A recent study on the proviral DNA sequences of *nef* from 12 HIV-infected patients with PAH has added to this theory. In this study, by ALMODOVAR *et al.* [32] these signature sequences were compared with the Los Alamos National Laboratory National Center for Biotechnology Information (NCBI) database of HIV-1 sequences (www.hiv.lanl.gov/content/sequence/HIV/mainpage.html; Los Alamos National Security, Los Alamos, NM, USA ); certain residues were more frequently found among the patients with HIV-PAH compared with historical controls. Further, when compared with the *nef* sequence in the SHIV-*nef* monkeys, there was commonality in three out of five amino acid substitutions [32]. These data further support the hypothesis that HIV-infected patients who develop PAH may be infected with a particular HIV-1 mutant strain that produces a distinct and pathology-inducing Nef protein. However, against Nef as the sole mediator of PAH, another group of investigators have found pulmonary arteriopathy in 11 out of 13 SHIV-*env*-infected macaques. Furthermore, and in notable difference from the prior SHIV-*nef* report, three of the 11 SIV-infected control monkeys also demonstrated pulmonary vascular lesions, thereby arguing against an absolute requirement for an HIV protein [33].

Although a number of studies implicate HIV proteins in the development of HIV-PAH, substantial research is still required to link a specific viral protein conclusively with the development of this complication of HIV infection. However, these investigations strongly support a viral factor as contributing to the pathogenesis of PAH. Whether it is only one viral factor, the combination of many different viral factors or viral factors in combination with other variables is still unknown.

## Host response and factors

Based on the current understanding of IPAH and other associated PAH, it is very likely that during an HIV infection, the biology of the host exerts significant influence in determining the predisposition to develop PAH. Two such genomic host factors are the *BMPR2* gene and the major histocompatibility complex (MHC) human leukocyte antigen (HLA) class II allele type. There is clear association between *BMPR2* gene mutations and an increased risk of developing PAH (HPAH). In some patients with IPAH, an association with MHC HLA class II alleles of the DR and

the DQ loci has been reported [34]. Both of these associations have been tested in HIV-infected patients. In a cohort of 82 HIV-infected patients with PAH, NUNES *et al.* [35] screened 19 patients and found no *BMPR2* mutations. In regard to HLA type, MORSE *et al.* [36] examined 10 racially diverse patients with HIV-PAH and identified an increased frequency of HLA-DR6-DR52, and of the linked alleles HLA-DRB1*1301/2, DRB3*0301and DQB1*0603/4 when compared with the uninfected Caucasian controls. These genotypes also differed in frequency from reports of patients with IPAH [34]. Thus, although *BMPR2* mutations do not appear to contribute to HIV-PAH, there may be HLA genotypes associated with increased risk of developing PAH if infected with HIV. However, these observations are significantly limited by the number of patients included in each study and are not yet conclusive.

Beyond genomic variables, other host variables, which could possibly contribute to the pathogenesis of PAH, have also been characterised. The relevance of many of these pathways in the pathogenesis of HIV-PAH is not yet clear; however, based on the clinical response to accepted PAH therapeutics, it is clear that certain host biology is integral. Primarily this is related to the molecules of vasomotor tone, such as ET-1, phosphodiesterase type-5 (PDE-5), prostanoids and NO. Although it is clear that pulmonary arterial tone is of great relevance, the principal pathology found in PAH is the obliterating foci of endothelial cells that define the plexiform lesions; therefore, endogenous mediators of proliferation have been examined in patients with PAH. A growth factor that has been studied in both PAH and HIV-PAH is platelet-derived growth factor (PDGF). PDGF, a polypeptide composed of homo- or heterodimers and secreted by many cell types, induces proliferation and has been identified in both inflammatory and myeloproliferative disorders [37–40]. Increased PDGF isoforms and receptors have been found in lung tissue from patients with PAH compared with lung tissue from individuals without PAH [18]. Lung tissue from patients with HIV-PAH has also been examined; despite a smaller number of samples, increased expression of PDGF has been found [18]. Further, there are a small number of reports describing the use of the tyrosine kinase inhibitor (TKI) imatinib mesylate, a selective antagonist of the PDGF receptor (FDGFR), for severe pulmonary hypertension refractory to conventional medications. These case reports and a recently completed phase III trial describe significant improvement in pulmonary haemodynamics and functional class with imatinib [41–43]. Thus, it is likely that the dysregulation of host PDGF and possibly other growth factors play a role in the development of HIV-PAH.

## Clinical presentation and evaluation of HIV-PAH

The clinical findings and the diagnostic approach to PAH have been well described [44]; in addition distinctive features for HIV-PAH have also been reported. In reviewing these reports it is important to remember that the majority of the case reports and series include patients from the pre-HAART era. Thus, these are clinical characteristics that are most applicable to cohorts with limited access to antiretrovirals; the utility of these clinical findings might be tempered in populations where HAART is widely available.

The majority of symptoms reported in HIV-PAH patients are related to right ventricular (RV) dysfunction and include dyspnoea on exertion (85%), pedal oedema (20–30%), non-productive cough (19%), fatigue (13%), syncope or near-syncope (12–30%) and chest pain (7–20%). The mean age of patients with HIV-PAH is $33 \pm 7$ years with a female-to-male ratio of 1:1.6; this differs from IPAH in which females predominate (female-to-male ratio reported between 1.7:1 and 3:1) [45, 46]. The symptoms of HIV-PAH are similar to those of IPAH; however, the interval between symptom development and diagnosis is shorter in the HIV-PAH population (6 months *versus* 2.5 years) [46]. This may be due to the increased medical surveillance of the HIV-infected patients or is possibly a reflection of a more rapid progression of the HIV-related disease. Overall survival in patients with HIV-PAH at 1, 2, and 3 years after PAH diagnosis was reported as 73%, 60%, and 47% respectively, substantially worse than those reported for patients with IPAH [45]. As in IPAH, there is reduced survival in patients with more severe New York Heart Association (NYHA)/WHO functional class.

The most frequently identified risk factors for HIV infection in patients with HIV-PAH are intravenous drug use (58%), homosexual contact (22%), haemophilia (9%), and heterosexual contact (9.2%) [16]. There is no correlation between the CD4 count, HIV viral load, or history of opportunistic infections and the occurrence of HIV-PAH [6, 16]. However, many investigators have found that patients with lower CD4 counts have more severe PAH disease [6, 34, 46].

More recently two studies of HIV-PAH patients treated during the HAART era have been published. In a cohort of 35 French patients [6], there was no significant difference from characteristics described in prior series; compared with HIV patients with dyspnoea but no PAH, HIV-PAH patients were predominantly male (71% *versus* 53%), *i.v.* drug users (51% *versus* 22%) and more patients had a CD4 <200 (37% *versus* 18%). Overall, CD4 counts did not differ significantly between the two populations. For all patients PAH was confirmed by right heart catheterisation (RHC); it was noted that the five recently diagnosed patients had a milder disease than those patients who had less recently been diagnosed (mean $\pm$ SD for pulmonary arterial pressure ($P$pa) $30 \pm 9$ *versus* $46 \pm 13$ mmHg, and pulmonary vascular resistance (PVR) was $4 \pm 3$ *versus* $10 \pm 4$ Wood units, respectively) [6]. However, because of the small number of patients in this study, these observations need to be confirmed.

The Swiss HIV cohort study has been actively collecting data since 1988; it recently reported on a cohort of 19 patients diagnosed after 2001 [8]. In this cohort, in comparison with those individuals who were diagnosed before 2001, the patients were older (mean age 43 *versus* 34 years, respectively), and had a higher median CD4 cell count (215 *versus* 169 cell·uL$^{-1}$). However, by other measures, this cohort resembled pre-HAART HIV-PAH patients, more males and *i.v.* drug users. Further characterisation of HIV-PAH patients in the HAART era is clearly warranted.

Some characteristics of this population were found in a recent retrospective analysis [47], 81% patients were receiving HAART, 79% had a CD4 count >200 cells·μL$^{-1}$, and 49% had an undetectable HIV load. 22% of the patients were NYHA/WHO functional class II, 69% were NYHA/WHO functional class III and 9% were functional class IV. The mean 6-minute walking distance (6MWD) was 375 m. Mean PVR was 689 dyn·s·cm$^{-5}$. In the study, all patients were treated with HAART. Patients who received PAH-specific treatment had an improvement in their 6MWD and haemodynamics. In patients who did not receive PAH-specific treatment improved, but their haemodynamic parameters did not change. Overall survival rate was 88% and 72% at 1 and 3 years, respectively. Multivariate analysis demonstrated that cardiac index >2.8 L·min$^{-1}$·m$^{-2}$ and CD4 cell count >200 cells·μL$^{-1}$ were independent predictors of survival. The authors concluded that antiretroviral therapy (ART) did not improve the haemodynamic parameters; prognosis was related to CD4+ cell counts and cardiac parameters.

Once the diagnosis of PAH is suspected in an HIV-infected person, it is essential to confirm pulmonary hypertension (PH) by RHC. Once PAH is confirmed, other comorbidities contributing to the development of PAH should be considered, for example contaminants in injected drugs, such as methylcellulose, which can induce extensive pulmonary arteriothrombosis leading to PH; likewise, chronic liver disease and portal hypertension associated with hepatitis B or C infection, commonly seen in the HIV-infected population, can lead to PH. However, by convention, HIV-infected patients with PH, even if they have a significant history of liver dysfunction or *i.v.* drug use, are considered to have HIV-PAH because it is impossible to distinguish which disease process contributed most to the development of PAH. In addition the treatment approach is the same as that for PAH.

## Treatment of HIV-PAH

Table 1 shows three selective studies of HIV–PAH patients and their therapy regimens. As with other forms of PAH, treatment of HIV-PAH is based on symptoms, NYHA/WHO functional class, the severity of PH and RV dysfunction. However, the impact of currently available PAH-specific therapies on clinical status and survival in the HIV-seropositive individual is not known [18, 49–51].

Moreover, there are no randomised, controlled studies of any PAH-specific treatment in patients with HIV-PAH.

## Calcium-channel blockers

The haemodynamic improvements with calcium channel blockers (CCBs) in IPAH have not been reproduced in HIV-PAH despite the pathological similarities of the diseases [52, 53]. Only a small subset of all IPAH patients had sufficient vasoreactivity to be considered for CCB therapy; perhaps this subset is smaller in HIV-PAH patients due to late presentation. Yet, those HIV-PAH patients with NYHA/WHO functional class I–III, who have a positive vasodilator response to NO adenosine, or prostacyclin, could be considered for CCB therapy. Oral anticoagulation to decrease *in situ* thrombosis has not been evaluated in HIV-PAH, but its use in patients with IPAH has often been extrapolated, rightly or wrongly, to those HIV-PAH patients without a contra-indication for anticoagulation (goal of an international normalised ratio (INR) 1.5–2.0).

## Prostanoids

### *Epoprostenol*

Continuous *i.v.* epoprostenol (prostacyclin) improves haemodynamics, 6MWD, functional class, quality of life, and survival in NYHA/WHO functional class III and IV patients with IPAH [54–59]. In a study of 19 patients with HIV-PAH, PETITPRITZ *et al.* [3] found that acute infusion of epoprostenol resulted in a 20% decrease in the PVR index (PVRI). A subsequent study of six patients with HIV-PAH also noted a significant improvement in haemodynamics with acute infusion [49]. Five out of the six patients underwent repeat cardiac catheterisation at 12 months (the sixth patient died of nucleoside analog-induced lactic acidosis) with four of these patients having additional improvement in $P_{pa}$, PVR (PVR), and cardiac output with chronic epoprostenol infusion. Three of these patients had further continued benefit or improvement in their PAH at catheterisation at 24 months [50]. In one of these original patients, there has been continued benefit with epoprostenol for >15 years (unpublished data).

In the largest series to date, NUNES *et al.* [35] described a single-centre, retrospective case series of 82 HIV-PAH patients, which included 20 NYHA/WHO functional class III or IV patients treated with epoprostenol. Due to the rapidly changing therapeutic standards over the 14-year study period, only a subset of patients was treated with a protease inhibitor or HAART. While the beneficial effects of epoprostenol, as defined by an improved 6MWD and improved haemodynamic

**Table 1.** Studies on patients with HIV-associated pulmonary arterial hypertension (PAH)

| | First author [ref.] | | |
|---|---|---|---|
| | PETIPRETZ [3] | NUNES [35] | DEGANO [48] |
| **Type of study** | Retrospective | Retrospective | Retrospective |
| **Recruitment period years** | 1987–1992 | 1986–2000 | 2002–2007 |
| **Patients included n** | 20 | 82 | 59 |
| **Medication available during study** | CCB | Epoprostenol | Bosentan |
| **Number of patients on medication** | Unknown | 20 received drug for 17±13 months | All |
| **Patients on PI plus two other antiretrovirals** | 0 | 48 | 83 |
| **Survival years** | | | |
| 1 | NR | 73 | 93 |
| 2 | 46 | 60 | 86 |
| 3 | NR | 47 | 66 |

Data are presented as %, unless otherwise stated. PI: protease inhibitor; CCB: calcium channel blocker NR: not recorded.

parameters, were durable at 17 months using multivariate analysis, only the CD4 count was independently associated with improved survival [35]. In addition to the well described adverse effects of epoprostenol, such as headache, flushing, jaw pain, nausea and thrombocytopenia, infection related to the need for chronic central venous access is a significant concern in the immunocompromised host [50, 60]. Despite this increased theoretical risk, there has been no documentation of increased incidence or severity of catheter-associated sepsis in HIV-PAH patients receiving epoprostenol. While a history of *i.v.* drug use may be a relative contra-indication to placement of a central venous catheter, we recommend epoprostenol, if appropriate, after a 6-month period of documented drug abstinence.

### *Treprostinil*

There is a single report of three patients with HIV-PAH who have been treated with subcutaneous treprostinil [61]. All patients were found to have an improvement in NYHA/WHO functional class and 6MWD (a minimum of 75 m) and all were alive at the 1 year follow-up. No adverse events requiring cessation of treatment were observed.

### *Iiloprost*

There are data on a small number of patients with HIV-PAH demonstrating acute and chronic efficacy of inhaled iloprost [62–64].

## Endothelin receptor antagonists

### *Bosentan*

A number of newer agents have been used for IPAH and demonstrated improvement in short-term measures, such as haemodynamics and exertional capacity. Although survival data are lacking, many of these agents are now being used in HIV-PAH. The oral ERA bosentan has been studied in small cohorts of HIV-PAH patients; these studies suggest that it may be beneficial. BARBARO *et al.* [65] compared 18 patients treated with HAART with 18 patients treated with HAART and bosentan. 24 weeks after initiating treatment the bosentan-treated group had a significantly increased 6MWD and decreased mean $P_{pa}$, PVR, and right atrial pressure ($P_{ra}$). Similar findings, increased 6MWD and haemodynamic parameters, were reported in a cohort of 16 HIV-PAH patients treated with bosentan for 16 weeks [66]. These observations have now been extended in a retrospective review of 59 patients with HIV-PAH treated with bosentan [48]. In this cohort, which included 12 of the 16 patients in the previous study [48], 56 patients were evaluated after 4 months of bosentan, and 38 were evaluated for a mean $\pm$ SD of 29 $\pm$ 15 months. Survival rates in this group at 1, 2 and 3 years were 93%, 86%, and 66%, respectively. This was in contrast to the previous data from 2003 in which survival rates were 73%, 60%, and 40% at 1, 2, and 3 years, respectively; and from 1994 in which survival rates were 46% at 2 years [2, 35]. However, it is important to differentiate the prevailing treatments available for HIV infection at the time when comparing these studies. For example, the percentage of patients receiving combination ART including a protease inhibitor was 83% in the 2009 study [48], 48% in the 2003 study [35] and 0% in the 1994 study [3].

A key limiting variable with bosentan is any active liver disease, since one of its potential side effects is transaminitis and liver injury. In Degano's cohort [47, 48], more than half of the patients (n=30) had concurrent hepatitis C (n=24) or B (n=6) infection, of which 10 had mild cirrhosis (Child–Pugh A class). In a univariate analysis of the data the authors found that neither hepatitis C nor B co-infections were associated with a poorer outcome. Three patients did discontinue bosentan due to elevated transaminases, but it is not clear whether any of these were hepatitis C- or B-infected patients. However, the frequency of elevated transaminases was no higher in HIV-PAH patients than in a recently reported cohort of 4,994 PAH patients treated with bosentan, in which the incidence of elevated transaminases was 7.6% over 30 months [67].

### *Ambrisentan*

There are no peer-reviewed data available on treatment of HIV-PAH with this ERA.

## Phosphodiesterase type-5 inhibitors

### *Sildenafil*

Other medications for the treatment of PAH are available and have potential use in HIV-PAH, some of which have been shown to improve haemodynamics, exercise capacity and NYHA/WHO functional class in patients with IPAH. Unfortunately, there are only limited studies of these agents in the treatment of HIV-PAH. Sildenafil, a selective phosphodiesterase type-5 inhibitor (PDE 5-I), has efficacy as monotherapy and in combination treatment in several small uncontrolled studies of patients with a variety of PAH aetiologies [68]. Case reports of patients with HIV-PAH treated with sildenafil demonstrate decreased $P_{pa}$ and improved clinical status [63, 69]. However, close consideration of potential interaction with concurrent antiretroviral medications is warranted since protease inhibitors can cause a significant increase in the levels of sildenafil and sildenafil can significantly decrease levels of protease inhibitors [70].

### *Tadalafil*

There are no peer-reviewed data available on treatment with HIV-PAH with this PDE 5-I.

## Algorithm of PAH-specific therapy in HIV-PAH

Due to the lack of randomised controlled trials in HIV-PAH, evidence-based guidelines are not currently available for PAH-specific therapy in HIV-PAH. As such, practitioners should follow the general guidelines for treatment for PAH. We currently recommend systemic prostanoids in NYHA/WHO functional class IV patients or in NYHA/WHO functional class III patients with a low cardiac index. In NYHA/WHO functional class II–III patients, we encourage entry into a clinical trial (if available), or treatment with an ERA (bosentan or ambrisentan) or a PDE 5-I (sildenafil or tadalafil). Ultimately, choice of these PAH-specific therapies depends on the patient's antiretroviral regime (particularly protease inhibitors), the existence of concomitant liver disease (many HIV patients are co-infected with hepatitis B and/or C), and the experience and expertise of the treating centre.

## Antiretrovirals

Although medical treatment of HIV-PAH has many similarities to that of treatment for IPAH, it differs significantly in that one postulated therapeutic intervention is the use of antiretrovirals that directly target what is hypothesised to be at least one of the factors in the pathogenesis of PAH in these patients. However, the impact of antiretrovirals on the clinical course of HIV-PAH is controversial. PUGLIESE *et al.* [71] reported a decreased incidence of HIV-PAH with nucleoside reverse transcriptase inhibitors (NRTI) (0.7%) compared with combination HAART therapy (2%). In a retrospective study, which included a cohort of 47 patients with HIV-PAH, it was observed that those treated with HAART had a significantly increased median duration of survival when compared with patients who had received no treatment or non-NRTIs (NNRTI) alone [72]. Small studies suggest the use of zidovudine or didansosine may have benefit on right heart function and HAART combinations including reverse transcriptase and protease inhibitors appear to decrease the mortality for HIV-related congestive heart failure [73]. There are also case reports of the benefits of protease inhibitor treatment of HIV infection on right heart function and haemodynamics [74]. However, the true effect of HAART on HIV-PAH is currently unknown; moreover, HIV-PAH is not considered as an indication for the initiation of HAART (in lieu of other indicators).

### *Statement of Interest*

None declared.

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# Chapter 8

# Pulmonary hypertension in children

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**SUMMARY: This review provides an overview of recent advances in the pathobiology, classification, and treatment strategies of paediatric pulmonary hypertension (PH). Current registries have begun to provide differences in aetiology and clinical course between adult and paediatric forms of PH. For example, in the majority of patients, PH in children is idiopathic or associated with congenital heart disease (CHD); PH associated with connective tissue disease (CTD) is rare in children. Recent studies of paediatric PH have highlighted unique aspects of the pathogenesis and challenging treatments in idiopathic pulmonary arterial hypertension (IPAH) or associated pulmonary arterial hypertension. Although treatment with new selective pulmonary vasodilators offers haemodynamic and functional improvement in paediatric populations, treatments in children still depend on results from larger adult studies and experience of clinicians treating children. Future studies are required for development of specific strategies for children with PH.**

**KEYWORDS: Classification system, heritable pulmonary arterial hypertension, idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with congenital heart disease**

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Pulmonary arterial hypertension (PAH) is an important cause of morbidity and mortality in children. PAH can present at any age from infancy to adulthood. The clinical features of paediatric PAH differ from those of adult disease. The distribution of aetiologies in children is quite different from that in adults, with a predominance of idiopathic cases (IPAH) or cases associated with congenital heart disease (CHD) [1, 2]. In paediatric populations, IPAH is usually diagnosed in its later stages due to its nonspecific symptoms. Without appropriate treatments, median survival rate after diagnosis of children with IPAH might be worse compared with that of adults [3]. However, there are currently limited data from randomised controlled trials in children with PAH for evaluating the safety and efficacy of vasodilator therapies, which are approved in adult patients. A recent randomised placebo-controlled clinical trial of sildenafil has highlighted the problems of conducting clinical trials in children and is discussed later in this chapter.

## Definition

A similar definition applies both to adult and paediatric populations with a biventricular circulation. PAH is defined as a mean pulmonary artery pressure ($P_{pa}$) greater than 25 mmHg, pulmonary capillary wedge pressure ($P_{pcw}$) less than 15 mmHg, and an increased pulmonary vascular resistance (PVR) (greater than 3 Wood units) [4]. In the adult definition, PVR has been removed. However, the definition of PAH in children or patients with CHD should include PVR, because patients with unrepaired CHD may have high $P_{pa}$ with high flow through a systemic-to-pulmonary shunt and low PVR, or high $P_{pa}$ with normal or diminished flow to the pulmonary circulation leading to high PVR [4]. Therefore, in patients with CHD, an elevation of PVR is a mandatory criterion. Pulmonary vascular disease affects not only patients with a biventricular circulation but also those with a single-ventricle circulation, which is palliated by direct connection of the superior and inferior vena cava to the pulmonary arteries. In patients with a total cavopulmonary circulation in which flow to the lungs is passive, PAH may be defined as a PVR greater than 3 Wood units or a transpulmonary gradient greater than 6 mmHg even if the mean $P_{pa}$ is less than 25 mmHg [5]. As neonates and infants may have a lower blood pressure than adults, PAH may also be described according to the ratio (greater than 0.5) of pulmonary artery systolic pressure/systemic artery systolic pressure, but this has not been validated.

## Classification

Classification of the forms of pulmonary hypertension (PH) was updated at the World Health Organization (WHO) conference in Dana Point in 2008 [6]. According to this current diagnostic classification, PAH is classified as group 1 PH. Group 1 includes PH that is idiopathic or heritable, associated with CHD, connective tissue disease (CTD), portal hypertension, HIV infection, drugs and toxins, or diagnosed as persistent pulmonary hypertension of the newborn. However, it may be difficult to classify all paediatric patients according to the adult classification. Although pulmonary vascular disease is a fatal condition and a crucial issue in paediatric patients with PAH, the Dana Point classification does not reflect the complex heterogeneity of factors that contribute to paediatric pulmonary vascular disease [6]. For example, bronchopulmonary dysplasia and congenital diaphragmatic hernia involve PH associated with abnormalities of lung hypoplasia, which are associated with the lung vasculature and airways, both of which develop *in utero*. A classification system of paediatric pulmonary hypertensive vascular disease has been proposed (table 1) [5]. In the new classification, paediatric hypertensive pulmonary vascular diseases are divided into 10 broad categories, from the neonate to adolescent. In particular, this classification recognises the concepts of the contribution of abnormalities of lung growth and development to paediatric pulmonary hypertension (fig. 1). The Panama classification system may improve diagnostic strategies, promote

**Table 1.** The broad schema of 10 basic categories of paediatric pulmonary hypertensive vascular disease

| Category | Description |
|---|---|
| 1 | Pre-natal developmental pulmonary hypertensive vascular disease |
| 2 | Perinatal pulmonary vascular maladaptation |
| 3 | Paediatric cardiovascular disease |
| 4 | Bronchopulmonary dysplasia |
| 5 | Isolated paediatric pulmonary hypertensive vascular disease (isolated paediatric PAH) |
| 6 | Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes |
| 7 | Paediatric lung disease |
| 8 | Paediatric thromboembolic disease |
| 9 | Paediatric hypobaric hypoxic exposure |
| 10 | Paediatric pulmonary vascular disease associated with other system disorders |

PAH: pulmonary arterial hypertension. Reproduced and modified from [5], with permission from the publisher.

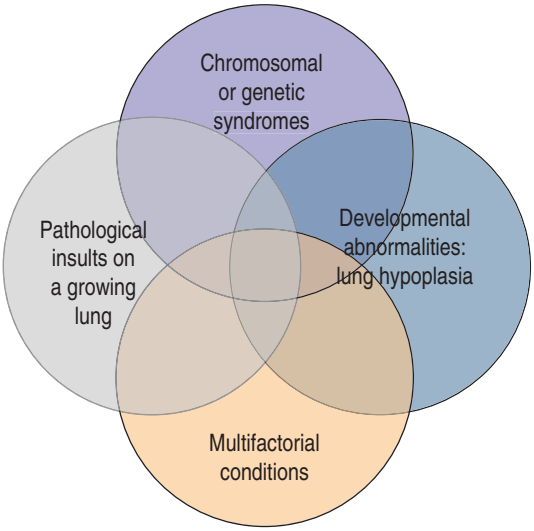
Chromosomal or genetic syndromes
Pathological insults on a growing lung
Developmental abnormalities: lung hypoplasia
Multifactorial conditions

**Figure 1.** The heterogeneity and multifactorial elements in paediatric pulmonary hypertensive vascular disease. Reproduced and modified from [5], with permission from the publisher.

clinical investigation and aid in understanding of the epidemiology of paediatric hypertensive pulmonary vascular disease.

## Epidemiology and aetiology

The landscape of paediatric PH has been further elucidated in the past year. In the Netherlands registry, the incidences of IPAH and PAH associated with CHD were 0.7 cases per million and 2.2 cases per million, respectively [7]. The most common causes of transient PH were persistant pulmonary hypertension of the newborn and PH associated with CHD requiring cardiac surgery with resolution of PAH after surgery, with incidences of 30.1 and 21.9 cases per million children, respectively (fig. 2) [7]. Female predominance in children with IPAH and heritable PAH has been reported [8]. However, there is no significant difference in sex balance in younger children compared with older children. IPAH (50–60%), heritable PAH (10%) and PAH associated with CHD (24–52%) account for the majority of the forms of PAH in paediatric populations [1, 2, 7, 9]. Additionally, familial PAH composes 6–12% of all cases of IPAH [10, 11].

A recent registry study (The Tracking Outcomes and Practice in paediatric Pulmonary Hypertension (TOPP) registry) presented demographic data from 362 paediatric patients with pulmonary hypertension [12]. Of the 362, 317 (88%) patients had IPAH, familial PAH and PAH associated with other disorders. Of these, IPAH or familial PAH was present in 182 (57%) and PAH associated with other disorders in 135 (43%), of whom 115 (85%) cases were associated with CHD. 42 (12%) patients had PH associated with respiratory disease or hypoxaemia, or with bronchopulmonary dysplasia. Only three patients had either chronic thromboembolic pulmonary hypertension (CTEPH) or miscellaneous causes of PH. Chromosomal anomalies, mainly trisomy 21, were reported in 47 (13%) patients. The median age at diagnosis was 7 years (interquartile range 3–12 years); 59% (268 out of 456) were female [12].

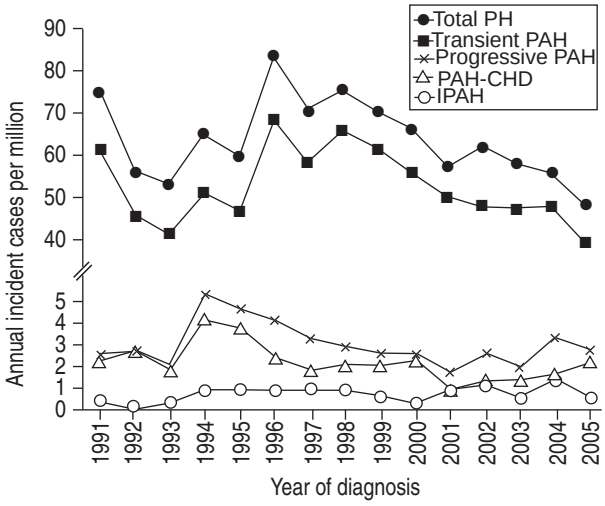


**Figure 2.** Annual incidence rates for paediatric pulmonary hypertension (PH) in the Netherlands. PAH: pulmonary arterial hypertension; CHD: congenital heart disease; IPAH: idiopathic PAH. Reproduced and modified from [7], with permission from the publisher.

## Pathogenesis

PAH is characterised by a complex arteriopathy consisting of intimal thickening and fibrosis, medial hypertrophy and hyperplasia, and adventitial change. Alterations in endothelial function are noted before structural changes, and include distal extension of smooth muscle into nonmuscular regions of the vasculature. Important proliferative mediators include increased thromboxane $A_2$ and endothelin-1 (ET-1), and decreased vasodilator and antiproliferative vasoactive

mediators, such as prostacyclin and nitric oxide (NO) [13, 14]. Recently, interest in stem cells/progenitor cells has enhanced our knowledge of the role of extravascular cells in the development of the fibroproliferative process. Endothelial progenitor cells (EPCs) contribute to vascular repair and new vessel formation [15, 16]. Circulating EPCs are a noninvasive marker of vascular damage, remodelling and dysfunction [17, 18]. Previous studies have examined the contribution of EPCs to the pathogenesis of PAH [19–22]. An open-label, non-randomised pilot trial showed that the transplantation of EPCs may improve exercise capacity, functional class and pulmonary haemodynamics in children with IPAH [22]. In contrast, mechanisms contributed by inflammatory cells in paediatric PAH have not been thoroughly investigated. Fibrocytes are characterised by expression of CD45 (leukocytes) and collagen and are recruited to sites of injury in persistent inflammatory remodelling and pro-angiogenic signalling [23, 24]. Fibrocytes are associated with poor prognosis in patients with idiopathic pulmonary fibrosis (IPF) [25]. Similarly, myeloid-derived suppressor cells (MDSCs) are increased in inflammatory disease and orchestrate immune cell responses. Recent published studies have evaluated circulating fibrocytes and MDSCs in 26 children with PAH compared with non-PAH controls [26, 27]. Circulating fibrocytes and MDSCs in children with PAH were increased compared to controls. Higher numbers of fibrocytes and MDSCs correlated to increasing $P_{pa}$. Fibrocytes and MDSCs may play an important role in the vascular remodelling in paediatric pulmonary hypertension (fig. 3).

## Genetics

Mutations in receptors of the transforming growth factor (TGF)-β receptor family have been identified in most cases of familial PAH and some cases of sporadic IPAH, and include abnormalities of the bone morphogenetic protein receptor type 2 (*BMPR2*) gene, activin receptor-like kinase (ALK)-1 and endoglin receptor genes [28, 29]. The TGF-β superfamily controls cell proliferation, migration, differentiation, apoptosis, and extracellular matrix secretion and deposition [30, 31]. Mutations of *BMPR2* are identified in approximately 50–70% of familial PAH patients and 10–40% of sporadic cases [32]. Previous studies have investigated the role of *BMPR2* mutations on acute vasoreactivity and disease severity in IPAH and familial PAH in children and adults [33]. Of 147 patients (78 children, 69 adults; 114 with IPAH, 33 with familial PAH), *BMPR2* mutations were indentified in 23 (16%) patients: eight (10%) out of the 78 children and 15 (22%) out of the 69 adults. *BMPR2* mutation-positive children are less likely to respond to acute vasodilator testing than mutation-negative children and appear to have more severe disease at diagnosis, although *BMPR2* mutations seem to have similar clinical implications in children and in adults with PAH. *BMPR2* mutations are uncommon in children with PAH and PAH associated with CHD [34]. ALK-1 mutations have been detected in adults and children with hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease) and co-existent PAH [11]. Endoglin is highly expressed during angiogenesis and is essential for ALK-1 signalling. Mutations in endoglin have been reported in patients with PAH [35].

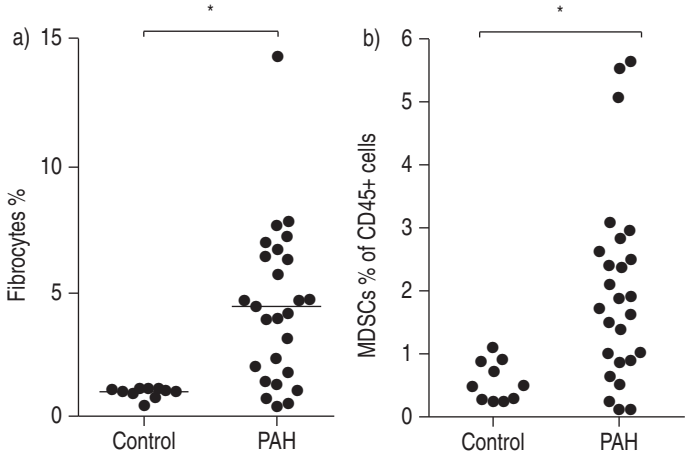


**Figure 3.** Circulating fibrocytes and myeloid-derived suppressor cells (MDSCs) in 26 children with pulmonary arterial hypertension (PAH) compared with 10 non-PAH controls. a) Fibrocytes in PAH patients increased in peripheral blood compared with controls (n=26, mean 4.24% *versus* n=10, mean 0.97%). b) MDSCs in PAH patients increased in peripheral blood compared with controls (n=26, mean 1.86% *versus* n=10, mean 0.57%). *: $p<0.05$ *versus* control. Reproduced from a) [26] and b) [27], with permission from the publishers.

## Clinical presentation

The clinical manifestations of PH are related to the degree of $P_{pa}$ and to right ventricular (RV) function. The presenting symptoms in children with PAH are highly variable and depend on the age at presentation. Although the overall clinical presentation of PAH in children is similar to that in adults, symptoms of PAH in children are unique. In IPAH, infants often present with poor appetite, failure to thrive, tachypnoea and irritability due to low cardiac output. Older children present with similar symptoms to adults and complain of exercise intolerance, such as dyspnoea on exercise and occasionally chest pain resulting from RV ischaemia. The most frequent initial presenting symptom in IPAH and PAH associated with CHD is dyspnoea on exertion [13, 36]. In paediatric patients with IPAH and heritable PAH, near-syncope and syncope are more common in children, while peripheral oedema is more frequently in adults. In addition, near-syncope or syncope is more frequent in IPAH and familial PAH patients compared to those with PAH associated with CHD [13, 36]. A history of syncope was less frequent in the group who had been diagnosed at the youngest age [13]. In IPAH or PAH associated with repaired CHD, hypoxic seizures may occur; thus, children are sometimes misdiagnosed with a seizure disorder. In contrast, syncope is a rare symptom in un-operated patients with Eisenmenger's syndrome. Patients with Eisenmenger's syndrome have deterioration of exercise tolerance and multiple organ disease due to secondary erythrocytosis and blood hyperviscosity. Haemoptysis, cerebrovascular accidents resulting from paradoxical emboli and arrhythmias are more common in Eisenmenger's syndrome patients [37].

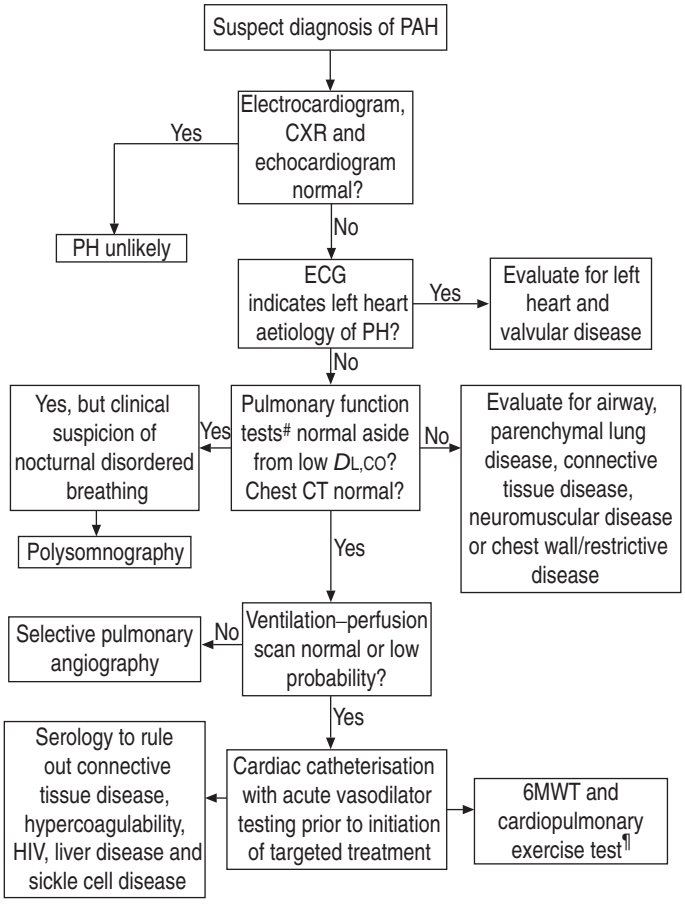
Suspect diagnosis of PAH
Electrocardiogram, CXR and echocardiogram normal?
Yes
PH unlikely
No
ECG indicates left heart aetiology of PH?
Yes
Evaluate for left heart and valvular disease
No
Yes, but clinical suspicion of nocturnal disordered breathing
Yes
Pulmonary function tests# normal aside from low DL,CO? Chest CT normal?
No
Evaluate for airway, parenchymal lung disease, connective tissue disease, neuromuscular disease or chest wall/restrictive disease
Polysomnography
Yes
Selective pulmonary angiography
No
Ventilation–perfusion scan normal or low probability?
Yes
Serology to rule out connective tissue disease, hypercoagulability, HIV, liver disease and sickle cell disease
Cardiac catheterisation with acute vasodilator testing prior to initiation of targeted treatment
6MWT and cardiopulmonary exercise test¶

**Figure 4.** Paediatric pulmonary arterial hypertension (PAH) diagnostic work-up. CXR: chest radiography; PH: pulmonary hypertension; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CT: computed tomography; 6MWT: 6-minute walk test. #: if unable to obtain a reliable test in a young child and there is a high index of suspicion for underlying lung disease, the patient may require further lung imaging; ¶: children >7 years of age can usually perform reliably to assess exercise tolerance and capacity in conjunction with diagnostic work-up. Reproduced and modified from [9], with permission from the publisher.

## Diagnosis

The general diagnostic evaluation in children is similar to that in adult patients. The diagnosis of IPAH is made when all other known causes of PH have been excluded. Figure 4 shows a general approach using a diagnostic algorithm [10, 38]. This chapter will focus on recent developments in the diagnosis of children with PAH. A recent review [10] discusses general diagnostic considerations.

### Cardiac catheterisation

Although noninvasive tests are useful in evaluating suspected PAH, cardiac catheterisation remains the gold standard for assessing the diagnosis and disease severity, and

evaluating treatment responses in children. Haemodynamic parameters have been shown to correlate with prognosis in adult patients and recently in children [36]. Elevated right atrial pressure (10 mmHg or higher), low cardiac index (2.1 $L \cdot min^{-1} \cdot m^{-2}$ or lower) and low central venous oxygen saturation (less than 64%) have previously been identified in patients at higher risk of death [39].

Acute vasodilator testing is essential to determine initial therapy in children. The recommended acute vasodilator drugs are short-acting vasodilators including inhaled nitric oxide (10–20 ppm) with oxygen or inhaled iloprost. A positive response to the vasodilator test in adult patients is defined as a reduction in mean $P_{pa}$ of at least 10 mmHg, reaching a maximum absolute value of 40 mmHg with unchanged or increased cardiac output [40]. In contrast, the paediatric criteria include a decrease in mean $P_{pa}$ of at least 20%, an increase or no change in cardiac index, and a decrease or no change in the ratio of PVR to systemic vascular resistance (SVR) [41–43]. The percentage of responders to this acute vasodilator testing is about 11–40% in children [41] and is about 6–27% in adult patients [11]. The probability of positive response may depend on age. Younger children are more likely to respond to acute vasodilator testing, although there is wide variability in paediatric patients [11, 40]. However, it is uncertain whether the same definition of vasoreactivity should be applied for adults and children.

A recent paediatric study (Registry to Evaluate Early and Long-Term PAH Disease Management (REVERAL)) has evaluated the difference in number of responders using paediatric response criteria between IPAH/familial PAH and PAH associated with CHD [36]. This study showed that 36 out of 102 IPAH/familial PAH patients (35%) were acute responders compared with nine out of 60 of those with PAH associated with CHD (15%; p=0.006) and the acute responders can have good long-term outcomes. Likewise, another recent study demonstrated the occurrence and prognostic value of acute vasodilator response in paediatric IPAH/heritable PAH, adult IPAH/heritable PAH, PAH-CHD and patients with/without a post-tricuspid shunt using three different pulmonary vasodilator response criteria [42]. The proportion of responders in IPAH/heritable PAH was higher than that in PAH associated with CHD (fig. 5). No responders were identified among those patients with a post-tricuspid shunt. However, the proportion of responders did not differ between paediatric and adult IPAH or heritable PAH. In addition, the acute vasodilator response was associated with improved survival [36, 42].

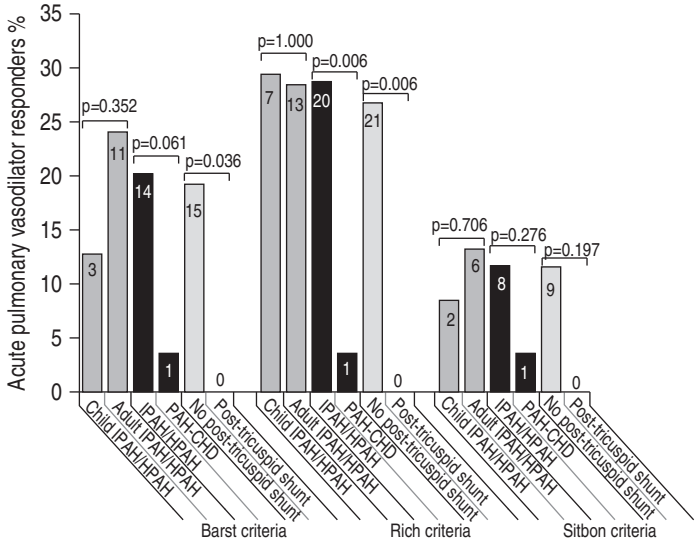


**Figure 5.** The number of acute pulmonary vasodilator responders according to the three criteria in use, in children *versus* adults with idiopathic (I)/heritable (H) pulmonary arterial hypertension (PAH); IPAH/HPAH *versus* PAH associated with congenital heart diseases (CHD); and patients without *versus* patients with post-tricuspid shunt, respectively. Figures in bars represent absolute numbers of patients. There were 14 (Barst criteria; 20%), 20 (Rich criteria; 29%) and eight (Sitbon criteria; 11%) acute responders in the IPAH/HPAH group, whereas there was one responder (11%) in the CHD group. The criteria used were as follows. Barst criteria [43]: decrease in mean pulmonary artery pressure ($P_{pa}$) of $\geqslant$20%, unchanged or increased cardiac index, and decreased or unchanged pulmonary-to-systemic vascular resistance ratio. Rich criteria, 1992 [44]: decrease in $P_{pa}$ and pulmonary to systemic vascular resistance of $\geqslant$20%. Sitbon criteria, 2005 [45]: decrease in $P_{pa}$ of $\geqslant$10 mmHg reaching a $P_{pa}$ value of $\leqslant$40 mmHg and an increased or unchanged cardiac output. Reproduced and modified from [42], with permission from the publisher.

## 6-minute walk test and cardiopulmonary exercise test

Exercise capacity has traditionally been assessed by 6-minute walk test (6MWT) with oxygen saturation monitoring in adults, with recent

application to paediatric patients, mainly in patients aged over 7–8 years. The serial change of 6-minute walking distance (6MWD) has been used for evaluating the clinical efficacy of current medications [46]. However, 6MWD has not been well characterised and may not be reproducible in children, whereas it correlates with outcomes in adult patients. Cardiopulmonary exercise testing is useful in evaluating children with PAH and is reliable in children aged over 7 years. Children with PH often have significant impairment in aerobic capacity and peak oxygen consumption [47].

### WHO functional class

Serial functional class assessments using the WHO functional classification are helpful. They are definitely useful in older children, but less so in infants or young children. The assessment of WHO functional class may be inadequate in paediatric patients with mild exercise intolerance and syncope. A functional classification system for children with PH has been proposed by the Paediatric Task Force of the Pulmonary Vascular Research Institute (table 2) [48].

## Treatment

In the past decade, specific targeted therapies have been developed and have improved survival in adult patients with PH recently. Survival within the 5 years after diagnosis was about 70–75% and was similar between IPAH or familial PAH and PAH associated with CHD (fig. 6) [36]. Novel targeted therapies have also improved survival in children, but the use of these agents is based on

**Table 2.** New functional classification for children with pulmonary hypertension (PH)

| Functional class | Description |
|---|---|
| I | This is defined, at all ages, as children with PH who are asymptomatic, growing and developing normally and have no limitation of physical activity. The emphasis on motor development in the first 2 years of life gradually shifts to the child's ability to interact with his/her peers, participate in sporting activities, and go to nursery and then school. |
| II | At all ages, children with PH are categorised as functional class II when they have only a slight limitation of physical activity due to fatigue and or dyspnoea but are comfortable at rest. Dyspnoea can interrupt feeding in young children. At this stage of their disease most children do not experience syncope or pre-syncope, but some children can do so while still having a good exercise tolerance. During the first 6 months of life they fall behind their developmental milestones but continue to grow along their own centiles. Infants and young children are readily fatigued and dyspnoeic when playing. Beyond age 2 years, it is important to assess attendance at school or nursery, which should be at least 75% that of healthy children. |
| IIIa | Functional class IIIa is characterised by marked limitation of physical activity. In addition to failing to achieve their developmental milestones, children between the ages of 6 months and 2 years may show regression of newly learnt activities. Inactivity is noticeable, the child being quiet and taking frequent naps. Less than ordinary activity, such as dressing, is tiring and can cause dyspnoea. Children frequently experience syncope and/or pre-syncope. Older children can become withdrawn and less confident, choosing to spend time with their families rather than their friends. Growth is compromised and appetite is poor. Nursery/school attendance is less than 50% of normal. The parents frequently say that the child has required excessive medical attention. |
| IIIb | In addition to the features characteristic of class IIIa, children in class IIIb often require supplemental feeding by nasogastric tube or gastrostomy. Older children can no longer go to school and although mobile at home they need a wheelchair when venturing outdoors. |
| IV | Children in class IV are severely compromised and unable to carry out any physical activity without fatigue and/or dyspnoea. They are frequently syncopal, may complain of chest pain and often become quiet and withdrawn. Signs of right heart failure are frequently present, particularly in teenagers. |

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experience more than clinical trials. Although PH related to CHD in most children may resolve after surgical correction, some children develop pulmonary vascular disease and develop irreversible pulmonary vascular disease. Unfortunately, there are limited data about treatment strategies in children with PH owing to the small number of randomised controlled clinical trials evaluating the safety and efficacy of specific treatments. Figure 7 shows a treatment algorithm in children with severe PAH [49].

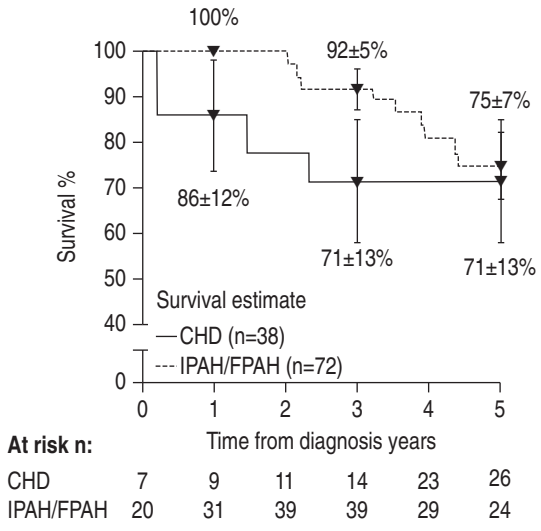


**Figure 6.** Survival within the 5 years from diagnostic right heart catheterisation for idiopathic (I)/familial (F) pulmonary arterial hypertension (PAH) and PAH associated with congenital heart disease (CHD). 5-year survival estimates (mean±SE) from diagnostic catheterisation for IPAH or FPAH and PAH associated CHD were 75±7% and 71±13%, respectively; hazard ratio p=0.53. Reproduced and modified from [36], with permission from the publisher.

## Prostacyclin

Epoprostenol is recommended as first-line treatment in severe PH in adult patients with WHO functional class III or IV [50]. Continuous intravenous epoprostenol therapy is also effective for improving symptoms, haemodynamics and survival in children with either IPAH or PAH associated with CHD [51]. Intravenous epoprostenol is initiated at 1–3 $ng \cdot kg^{-1} \cdot min^{-1}$ and gradually increased by 1–2 $ng \cdot kg^{-1} \cdot min^{-1}$ every 1–2 weeks if tolerated [52]. The target dose in children is usually 50–80 $ng \cdot kg^{-1} \cdot min^{-1}$. Long-term *i.v.* epoprostenol has improved survival for children with PAH, with a 4-year survival rate of 94% in IPAH [51].

Treprostinil may be used as treatment *via* three different routes of administration: subcutaneous, *i.v.* and inhaled. Recent studies have shown favourable experiences of switching from epoprostenol to subcutaneous or *i.v.* treprostinil therapy in children because of its stability at room temperature and longer half-life compared to epoprostenol [53–55]. Subcutaneous therapy has been used in small children [56]. Patients with an exceptional long-term response to *i.v.* therapy may be considered for transition to oral therapy with or without inhaled prostacyclin therapy [57]. Inhaled treprostinil may be used as add-on therapy or used for patients who have injection site pain due to subcutaneous infusion, if the dose of *i.v.* therapy can be weaned to less than 15 $ng \cdot kg^{-1} \cdot min^{-1}$ [58].

Iloprost is an inhaled prostacyclin analogue, and offers several advantages over *i.v.* epoprostenol infusion therapy, including less risk of systemic hypotension and minimised effect on ventilation/perfusion mismatch [59]. In previous paediatric studies, haemodynamics and WHO functional class were improved in some patients treated with iloprost [60, 61]. However, disadvantages may include reduced compliance, as iloprost is given six to nine times a day. Furthermore, clinical deterioration and side-effects such as lower airway reactivity may limit its use in children. Intravenous iloprost has been used in Europe with good results.

## Phosphodiesterase type-5 inhibitors

Phosphodiesterase type-5 inhibitors (PDE-5 I), including sildenafil and tadalafil, have been approved for PH therapy in adult patients. These PDE-5 I are administered orally, are tolerated well and do not require intensive monitoring. Recent studies have demonstrated that sildenafil is well tolerated among adults and children with IPAH and PAH associated with CHD [62–64]. Although sildenafil is approved for use in children with PAH in Europe (10 mg *t.i.d.* in patients weighing 20 kg or less, and 20 mg *t.i.d.* in patients weighing more than 20 kg), it is not approved for children with PAH in the USA. STARTS-1, the first study of its kind in children, was a randomised, double-blind

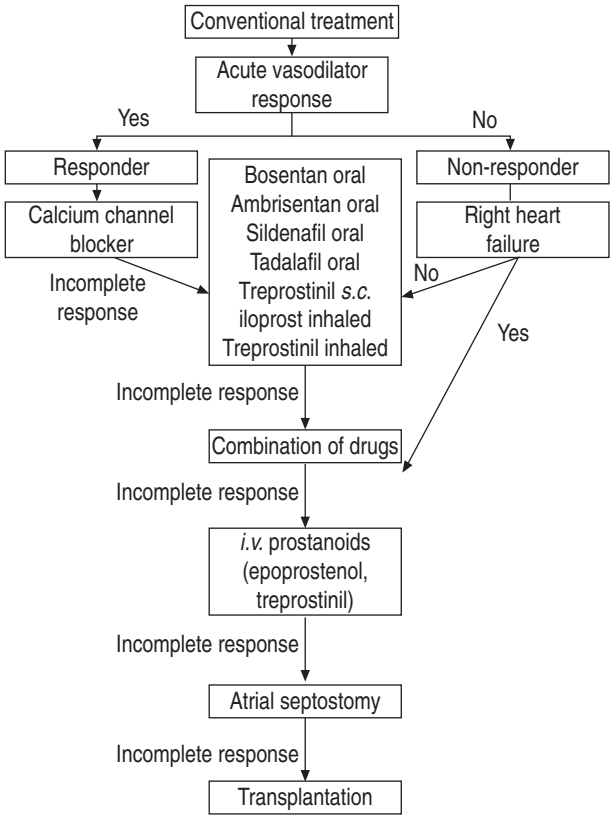


**Figure 7.** Treatment algorithm in children with severe pulmonary arterial hypertension. *s.c.*: subcutaneous. Reproduced and modified from [49], with permission and modified from the publisher.

placebo-controlled study [64]. In the 16-week study of treatment-naïve children, 234 children with PAH received low-, medium- or high-dose sildenafil, or placebo, orally three times daily. Peak oxygen uptake ($V'O_2$), functional class, $P$pa and PVR index (PVRI) improved with the medium- and high-dose groups *versus* placebo, while the low dose was ineffective. For the primary end-point, the estimated mean $\pm$SE change in peak $V'O_2$ for the low-, medium- and high-doses combined *versus* placebo was $7.7 \pm 4.0\%$ (95% CI -0.2–15.6%; $p=0.056$) (fig. 8). A long-term extension study included children continued on sildenafil monotherapy. For the first 2 years, survival on sildenafil monotherapy was similar for all dosage groups. At 3 years, an increase in mortality was noted at the higher doses, and the data safety monitoring board requested a decrease in the dose. Deaths in the extension study were related to aetiology and baseline disease severity. The majority of deaths occurred in patients with IPAH and familial PAH. Of patients who died, most had baseline values above median for PVR, mean $P$pa, and right atrial pressure. Intravenous sildenafil has also been studied. A double-blind, multicentre, placebo-controlled study of *i.v.* sildenafil has been conducted in paediatric patients with CHD and post-operative PH and showed favourable results, such as shorter time to extubation and intensive care unit stay, although the study was stopped early due to poor enrolment [65].

Tadalafil, a long-acting PDE-5 I, is a once-daily dosing drug. Tadalafil is currently approved for the treatment of adult patients with PAH. In adults, a placebo-controlled study demonstrated that tadalafil improved exercise capacity, time to clinical worsening and health-related quality of life in adult patients with IPAH or associated PAH [66]. Although tadalafil is recommended for PAH treatment in adult patients, little is known of its use in children with PAH. A recent study demonstrated clinical safety and efficacy of tadalafil therapy in 33 paediatric patients with PAH [67]. In this study, 29 out of 33 patients were switched from sildenafil to tadalafil. The average doses of sildenafil and tadalafil were $3.4 \pm 1.1$ and $1.0 \pm 0.4$ mg·kg$^{-1}$·day$^{-1}$, respectively. In 14 out of 29 children transitioned from sildenafil to tadalafil, repeat cardiac catheterisation showed statistically significant improvements in mean $P$pa ($53.2 \pm 18.3$ *versus* $47.4 \pm 13.7$ mmHg, $p<0.05$) and PVRI ($12.2 \pm 7.0$ *versus* $10.6 \pm 7.2$ wood units·m$^2$, $p<0.05$). Daily-dose tadalafil may improve compliance in children.

## Endothelin receptor antagonists

Bosentan, a dual endothelin receptor antagonist, is approved for use in adults with PAH but is not currently approved in children. Bosentan therapy was well tolerated and improved haemodynamics in a cohort of children with IPAH and PAH associated with CHD [67–71]. A retrospective study of 86 children on bosentan for a median exposure of 14 months with and without concomitant therapy

found that bosentan provided a sustained clinical and haemodynamic improvement and was overall well tolerated, and found 2-year survival estimates of 91% [68]. Follow-up of these patients at 4 years revealed the Kaplan–Meier estimate of disease progression in patients while on bosentan was 54%, with a survival estimate of 82% [69]. In a cohort of children with IPAH and PAH associated with CHD, the Kaplan–Meier survival estimates for 101 patients treated with bosentan as part of an overall targeted pulmonary hypertension strategy were 96%, 89%, 83% and 60% at 1, 2, 3 and 5 years, respectively [70]. In 146 children with PAH, elevated transaminase levels were reported in 2.7% of children compared with 7.8% of patients aged 12 years and over, and the overall discontinuation rate from bosentan was 14% in children compared with 28% in patients aged 12 years and over [2]. The prospective FUTURE-1 trial treated children with a paediatric-specific, water-soluble formulation at doses of 2 mg·kg$^{-1}$·dose$^{-1}$ and 4 mg·kg$^{-1}$·dose$^{-1}$ twice daily [71]. There was no difference in drug exposure, and plasma concentrations did not reach adult levels with either dose. There were no abnormalities of liver function testing, leading to a general recommendation of the 2 mg·kg$^{-1}$·dose$^{-1}$ twice daily for children. Bosentan, and other advanced therapies, have been associated with improved survival in adults with Eisenmenger's syndrome [72–74]. A specific paediatric formulation of bosentan has recently been approved in Europe.

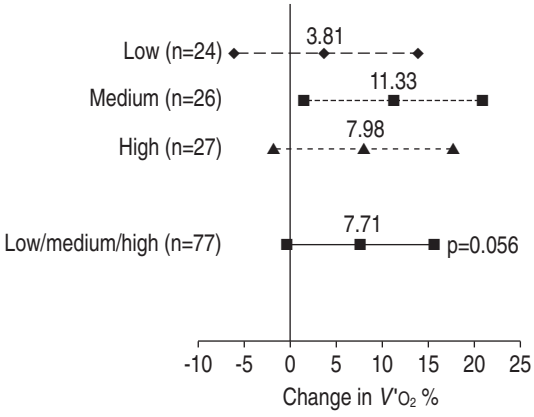


**Figure 8.** Peak oxygen uptake ($V'_{O_2}$) (% change from baseline to week 16) in three different dose regimens of sildenafil in comparison to placebo (n=29). At week 16, mean peak $V'_{O_2}$ was 18.4, 20.4, and 19.0 mL·kg$^{-1}$·min$^{-1}$ for the low-, medium- and high-dose groups, respectively, *versus* baseline values of 17.4, 18.0 and 17.4 mL·kg·min$^{-1}$, respectively. Placebo mean peak $V'_{O_2}$ was 20.0 mL·kg$^{-1}$·min$^{-1}$ at baseline and at week 16. The placebo-corrected estimated mean ± SE change in peak $V'_{O_2}$ from baseline to end of treatment for the low-, medium-, and high-dose groups combined was 7.7±4.0% (95% CI -0.2–15.6%; p=0.056). Reproduced and modified from [64], with permission from the publisher.

Ambrisentan is highly selective for the endothelin receptor ETA, and is approved in adult [75–77]. In children with PAH, the clinical efficacy, safety and pharmacokinetics of ambrisentan therapy have been studied recently [78, 79]. In a retrospective study, 38 paediatric PAH patients treated with ambrisentan have been evaluated [79]. 15 out of 38 patients were switched from bosentan to ambrisentan. The remaining 23 children were treated with ambrisentan as an add-on therapy due to disease progression. In both transition and add-on cases, mean $P_{pa}$ significantly improved (transition: 55±18 *versus* 45±20 mmHg, n=13, p=0.04; add-on: 52±17 *versus* 45±19 mmHg, n=13, p=0.03) during follow-up. WHO functional class improved in 31% of patients, but one patient required an atrial septostomy due to disease progression during follow-up (median (range) 20 (4–44) months). Although five (13%) patients discontinued ambrisentan due to severe headache, lack of clinical efficacy or near-syncope, no patients had aminotransferase abnormalities and there were no deaths after initiation of ambrisentan during follow-up [79].

## Combination therapy

In patients with advanced disease, combination therapy is appealing as multiple pathways are targeted. However, few studies have shown a definitive benefit. The PACES study confirmed that the addition of sildenafil to *i.v.* prostacyclin decreased the time to clinical worsening at initiation of *i.v.* therapy in adults with severe PAH [80]. Combination therapy is frequently used in children despite the lack of evidence. In the REVEAL registry, 41% of children with PAH were treated with monotherapy, whereas dual therapy (30%) or triple therapy (13%) was used in many patients.

### Goal-oriented therapy in children

The goals of treatment and follow-up in adult populations have not been applied to younger children. The following markers are appealing to use in children: clinical symptoms, exercise testing including measurement of peak $V'O_2$, biochemical markers such as brain natriuretic peptide (BNP) or N-terminal (NT)-pro-BNP, echocardiographic data, and WHO functional class [42, 81–83].

## Conclusion

PAH in children differs from PAH in adults. First, the classification of paediatric PH differs from that in adult patients, as young children frequently have abnormalities of lung growth. Secondly, it may be difficult to diagnose and assess disease severity due to the inability of younger children to perform exercise tests. Thirdly, pulmonary vascular disease is present in patients with a single ventricle without a pumping chamber to the lung. Treatment in children is based on experience whereas treatment in adults with PAH is based on clinical trials. Future studies are required for development of specific strategies for children with PH.


### *Statement of Interest*

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# Chapter 9

# Chronic thromboembolic pulmonary hypertension

*Diana Bonderman and Irene M. Lang*

**SUMMARY: Chronic thromboembolic pulmonary hypertension (CTEPH) results from mechanical obstruction of (major) pulmonary vessels by non-resolving thromboemboli. If left untreated, the condition is fatal due to increased right ventricular afterload and right heart failure. Recent advances in the understanding of misguided thrombus resolution, small-vessel pulmonary arteriopathy and the identification of CTEPH risk factors have introduced novel disease concepts. In this chapter, we assemble the relevant literature into a picture of the old and new views of CTEPH evolution. Moreover, the role of established as well as experimental diagnostic tools is reviewed, with an emphasis on imaging techniques that allow visualisation of perfusion defects and differentiation between thromboembolic and non-thromboembolic pulmonary vascular disease. Finally, therapeutic options are discussed. Pulmonary endarterectomy (PEA) is the treatment of choice in patients with confirmed CTEPH. After successful PEA, patients are considered cured, since a vast majority nearly normalise their haemodynamic parameters and exercise capacity. Data on medical treatment of the condition and evidence-based knowledge are put into perspective with current clinical practice.**

**KEYWORDS: Chronic thromboembolism, diseases of pulmonary circulation, pathomechanisms, pulmonary heart disease, surgical and medical therapy**

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Recent advances in the understanding of basic mechanisms and clinical course of chronic thromboembolic pulmonary hypertension (CTEPH) have shed new light on this enigmatic orphan condition and have challenged dogmatic views on the pathogenesis of this disease.

Traditionally, a strict line was drawn between the pathobiological processes underlying CTEPH and non-thromboembolic pre-capillary pulmonary arterial hypertension (PAH). In contrast to PAH, which is attributed to small-vessel arteriopathy and obliteration, CTEPH was thought to result from mechanical obstruction of the pulmonary vascular bed by organised fibrotic thromboemboli. However, current understanding of CTEPH is that of a dual vascular disorder, comprising a major-vessel thromboembolic vascular remodelling process and a small-vessel arteriopathy that is histologically indistinguishable from the pulmonary arteriopathy of PAH [1]. In agreement with this observation, no correlation could be found between the extent of

pulmonary arterial thromboembolic obstructions and pulmonary vascular resistance (PVR) [2]. One example of a condition that is associated with an overlap between classical ''major-vessel'' CTEPH and CTEPH ''small-vessel disease'' is splenectomy, which may lead to classical CTEPH but also to clinical presentations of PAH.

Moreover, the purely ''coagulatory'' concept of CTEPH as an uncontrolled thromboembolic state characterised by massive thrombosis and recurrent thromboembolic events has also been abandoned. A growing body of evidence suggests that in affected patients, minor or major thromboemboli do not resolve under conditions of concomitant inflammation, infection or malignancy, thereby leading to major vessel fibrosis and small-vessel remodelling [3–5].

In recent years, novel insights have affected our clinical routine. While the primary treatment remains surgical pulmonary endarterectomy (PEA), a recently published prospective CTEPH registry has illustrated that almost 40% of patients were not suitable for surgical removal of pulmonary thromboemboli [6]. Based on the concept that small-vessel arteriopathy is a major contributor to CTEPH evolution, vasodilator therapies may be useful alternatives for patients who are not suited for PEA. Although the BENEFiT (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension) study [7], as the first multi-centre randomised controlled trial of the dual endothelin receptor antagonist (ERA) bosentan, failed to achieve the second co-primary end-point, the availability of novel vasodilators and adaptive study designs may open new perspectives on medical treatment of inoperable CTEPH patients. Uncontrolled reports of parenteral prostacyclins in severe patients have indicated a survival benefit [8, 9].

## Definition

CTEPH is diagnosed if the following observations are made after at least 3 months of effective anticoagulation: 1) mean pulmonary arterial pressure ($P_{pa}$) exceeding 25 mmHg with a pulmonary capillary wedge pressure ($P_{pcw}$) equal to or less than 15 mmHg; and 2) one or more mismatched segmental or larger perfusion defects detected by ventilation/perfusion ($V'/Q'$) lung scan/multidetector computed tomography pulmonary angiography (CPA)/conventional pulmonary angiography [10].

## Epidemiology and prognosis

The exact incidence and prevalence of CTEPH are unknown. Current data derived from registries suggest that CTEPH occurs at an incidence of 3–30 cases per million in the general population. Classical estimates of disease prevalence refer to the number of CTEPH cases per survived pulmonary thromboembolic event [11–18] and report cumulative incidences between 0.1% and 9.1%. A significant number of patients develop CTEPH after asymptomatic or mildly symptomatic venous thromboembolic events, or in the absence of any clinically apparent venous thromboembolism (VTE) [19]. If left untreated, 3-year survival after CTEPH diagnosis has been reported as 78–85% in affected patients from Japan [20] and 70% in inoperable *versus* 76% in operable patients within the UK ($p=0.023$) [21]. For comparison, contemporarily treated patients with idiopathic, familial or anorexigen-associated PAH face a 3-year survival of 69.6% [9].

## Pathophysiology

CTEPH evolution is triggered by thrombotic obstruction of the pulmonary vascular tree by single or repetitive thromboembolic events arising from sites of venous thrombosis. Typically, it appears that thrombi fail to resolve and undergo a fibrotic organisation process with concomitant positive vascular remodelling in the major vessel compartment, and a negative vascular remodelling process in the resistance arteries. Progressive rarefication of the pulmonary vascular bed leads to a gradual rise in PVR, increased right ventricular (RV) afterload and right heart failure.

Although CTEPH is understood as a thromboembolic disorder, neither classical plasmatic risk factors for VTE nor defects in the fibrinolytic system have been identified in affected patients. For example, a deficiency of antithrombin, protein C and protein S, the G20210 mutation of prothrombin and hyperhomocysteinaemia are not associated with CTEPH. Furthermore, the factor V R506Q mutation (factor V Leiden) is not found to be more common in CTEPH patients [22]. However, in a recent retrospective study, factor V Leiden was significantly more common in CTEPH patients than in those with other forms of PH and the prothrombin mutation occurred more often in CTEPH patients, although the difference was not statistically significant [23]. Only lupus anticoagulant/antiphospholipid antibodies and the coagulation factor VIII, both well-known prothrombotic risk factors for VTE, have been found in a significant proportion of CTEPH patients in a majority of studies [3, 5, 10, 22–24].

No functional defects in the pulmonary vascular fibrinolytic system [25, 26] or gene polymorphisms [27] were found. Neither alterations in plasma levels of type 1 plasminogen activator inhibitor nor tissue-type plasminogen activator could be linked with CTEPH [28].

In recent years, attentive studies of large cohorts with pulmonary hypertension (PH) have demonstrated a clear association between distinct medical conditions and the occurrence of CTEPH. These have generated novel pathomechanistic hypotheses and set the stage for innovative experimental research. Our current understanding is that populations at increased risk for CTEPH are those with a history of splenectomy [3, 5, 29, 30], carriers of ventriculo-atrial shunts for the treatment of hydrocephalus or carriers of pacemakers with a history of device infection [3, 5], patients with inflammatory bowel disease [3], patients undergoing thyroid hormone replacement [5], patients with circulating antiphospholipid antibodies [5, 22, 24], patients who have survived cancers [5], individuals with non-0 blood types [5, 31], individuals with elevated plasma coagulation factor VIII [31], and carriers of the fibrinogen Aα Thr312Ala polymorphism (table 1) [27].

A large European prospective registry containing clinical and epidemiological data of 679 newly diagnosed CTEPH cases was closed in January 2009 [6]. In an ongoing project, registry data are analysed with respect to CTEPH risk factors. Results are expected later this year and will add a significant puzzle piece to our current knowledge on CTEPH risk factors.

Patients with ventriculo-artrial shunts and a history of device infection are at increased risk for CTEPH [3, 5]. It is well known that *Staphylococcus aureus* or *Staphylococcus epidermidis* are responsible for up to one-half of these infections [34], leading to thrombosis and device failure [35]. Molecular analysis of PEA specimens harvested from patients with CTEPH associated with ventriculo-artrial shunt infection uncovered staphylococcal DNA in a majority of samples [4]. In a

**Table 1.** Overview of risk factors for chronic thromboembolic pulmonary hypertension (CTEPH)

| Risk factor [ref.] | OR (95% CI) |
|---|---|
| **Infected ventriculo-artrial shunt/pacemaker [3, 5]** | 13.0 (2.5–129), 76.4 (7.7–10351) |
| **Splenectomy [3, 5]** | 13.0 (2.7–127), 17.9 (1.6–2438) |
| **Recurrent VTE [5]** | 14.5 (5.4–43.1) |
| **Thyroid disease [5]** | 6.1 (2.7–15.1) |
| **Previous VTE [5]** | 4.5 (2.4–9.1) |
| **Antiphospholipid antibodies [5]** | 4.2 (1.6–12.2) |
| **Survived cancer [5]** | 3.8 (1.5–10.4) |
| **Inflammatory bowel disease [5]** | 3.2 (0.7–16.0) |
| **Blood groups non-O [5]** | 2.1 (1.1–3.9) |
| **Fibrinogen Aα Thr312Ala polymorphism [27]** | 1.7 (1.1–2.5) |
| **HLA-B*5201 [32, 33]#** | 2.1 (1.3–3.6), 2.5 (1.6–3.9)¶ |
| **HLA-DPB1*0202 [32, 33]#** | 3.4 (1.7–6.7), 5.1 (2.5–10.2)¶ |
| **IKBL-p*03 [33]#** | 2.3 (1.5–3.7)¶ |

VTE: venous thromboembolism; HLA: human leukocyte antigen; IKBL: inhibitor of nuclear factor-κB-like. #: studies conducted in Japan; ¶: odds ratio for VTE-negative CTEPH.

murine model of stagnant-flow venous thrombosis, infection with *S. aureus* delayed thrombus resolution and led to an upregulation of profibrotic genes, including transforming growth factor (TGF)-β and connective tissue growth factor [4]. Moreover, experimental work in recent years suggests that thrombus angiogenesis, a key driver of thrombus resolution, may be impaired in CTEPH [36–40].

Small-vessel pulmonary vascular remodelling mainly affects unobstructed pulmonary vascular areas and is histologically indistinguishable from other forms of PH [1]. There is a broad individual range with respect to the degree of secondary small-vessel arteriopathy, which is clearly independent from thrombus burden [2], but may be related to the duration of the disease. It is still unclear whether it is individual susceptibility or thrombus composition, or both factors together, that determine the degree of small-vessel disease. Mutations in the bone morphogenetic protein receptor type II gene (*BMPR2*) that have been linked to the development of pulmonary vascular disease in familial or heritable PAH [41, 42] could not be related to CTEPH [43]. Interestingly, CTEPH patients with typical predisposing medical conditions, such as a history of splenectomy, ventriculo-artrial shunt, inflammatory bowel disease or osteomyelitis, face an adverse outcome when compared with other CTEPH patients [5]. This finding has been attributed to more severe small-vessel disease, although the exact mechanisms remain unclear.

The current pathomechanistic model of misguided thrombus resolution in pulmonary arteries of CTEPH patients is summarised in figure 1. Taken together, the initial trigger for CTEPH evolution is thought to be a thromboembolic event that may or may not be symptomatic. Concomitant inflammatory processes may cause fibrotic transformation of thrombus tissue. The potent fibrinolytic system of the lungs [44] fails to remove thrombus that is transformed into collagenous tissue. Fibrous obstructions grow by further *in situ* apposition of thrombotic material that is due to local imbalances of haemostasis [45]. Less obstructed resistance vessels undergo remodelling processes, *i.e.* small-vessel arteriopathy.

## Clinical presentation

Like patients with other forms of PH, CTEPH patients suffer from symptoms of progressive right heart failure. However, unless a significant degree of heart failure is present, the clinical manifestation of which is unremarkable. At early stages, typical complaints are exertional dyspnoea, fatigue and rapid exhaustion. At more advanced stages, signs and symptoms of overt right heart failure, such as resting dyspnoea and fluid retention, are predominant. Physical findings in earlier stages are subtle and may include a prominent pulmonary component of S2, left parasternal heave and a systolic murmur, if tricuspid regurgitation is present. At later stages, physical examination may reveal distended neck veins, leg oedema, ascites, hepatomegaly and acrocyanosis. A typical but rare clinical finding is bruits over peripheral lung fields [46]. This acoustic phenomenon is thought to occur in approximately 10% of CTEPH patients and has been attributed to turbulent flow in partially occluded pulmonary vessels [47].

Despite similarities in clinical presentation, the course of CTEPH is clearly different from PAH. There is a significant difference with respect to age at disease onset. On average, CTEPH patients are 7 years older when the disease is diagnosed, with a vast majority of patients presenting between their sixth and seventh decades [5]. In contrast to a progressive course of disease in PAH, CTEPH progresses episodically. A thromboembolic event that may be symptomatic or not is typically followed by a so-called honeymoon period that is characterised by an absence of symptoms or by mild symptoms. Episodes of desaturation and deterioration occur, interrupting apparent health.

## Diagnosis

In contrast to other subtypes of pre-capillary PH, CTEPH is amenable to surgery. Patients subjected to successful PEA regain a near-normal functional capacity with normal haemodynamics [48].

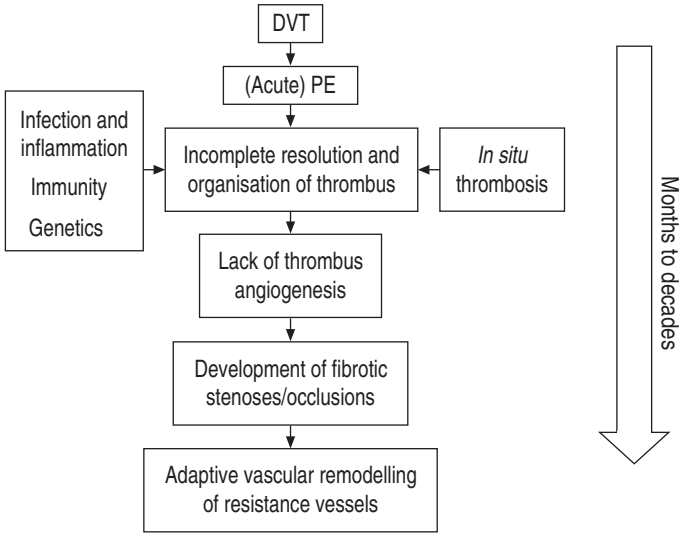


**Figure 1.** Pathophysiological concept of chronic thromboembolic pulmonary hypertension. DVT: deep vein thrombosis, PE: pulmonary embolism.

Therefore, the main goal of the diagnostic work-up of patients with an established diagnosis of pre-capillary PH is to test for the presence of thrombotic obstructions in major pulmonary arteries. Careful diagnostic work-up is crucial for the choice of optimal treatment. If CTEPH is suspected, patients should be referred to specialised expert centres with an experienced team of PH specialists, radiologists, anaesthetists and surgeons.

Imaging has become central to the diagnosis of CTEPH [49] and is guiding surgical accessibility of the obstructions. While visualisation of thrombus site and burden may serve as a surgical road map, the determination of operability is complex and hardly standardised. Major determinants of operability are thrombus localisation, PVR, relationship between haemodynamic compromise and thrombus burden, status of the lung parenchyma, previous cardiothoracic surgeries, comorbid conditions, unilateral *versus* bilateral disease, the response to nitric oxide (NO) during acute vasoreactivity testing [50], upstream resistance [51], and plasma levels of biomarkers, *e.g.* asymmetric dimethylarginine [5] or heart-type fatty acid-binding protein [52].

In PEA centres, available imaging techniques are used in a complementary fashion. Traditionally, $V'/Q'$ scanning and pulmonary angiography have been key tools for the assessment of CTEPH. An attractive logistic approach is to combine invasive diagnostic techniques, *i.e.* right heart catheter and pulmonary angiography, in a one-stop shop. In the light of technological advances, multidetector CTA and magnetic resonance angiography may supersede traditional imaging techniques. However, in current European practice, all imaging modalities are employed [6] to distinguish CTEPH from chronic obstructive pulmonary disease (COPD) with left subacute pulmonary embolism, cardiomyopathy, idiopathic PAH (IPAH) of the elderly or pulmonary veno-occlusive disease (PVOD).

## Right heart catheterisation

The diagnosis of pre-capillary PH is made by right heart catheterisation (RHC). Advanced techniques relying on invasive haemodynamic assessment have proven useful for quantification of concomitant pulmonary vascular disease, which is a strong predictor of adverse surgical outcome in patients with CTEPH [50, 51]. Secondary vascular disease is escaping current imaging algorithms because of their still-limited spatial resolution [47]. Analysis of pulmonary arterial occlusion pressure waveforms may be used for partitioning PVR, thus estimating the upstream contribution of resistance to total PVR. Pre-operative assessment of upstream resistance in 26 CTEPH patients predicted post-operative total pulmonary resistance index as well as mean $P_{pa}$ [51]. In a more recent study, our group demonstrated that acute vasoreactivity testing with inhaled NO may unmask the functional status of the pulmonary microvasculature and, thereby, predict surgical outcome [5].

## Ventilation/perfusion scanning

$V'/Q'$ scanning is the key imaging tool in the diagnostic work-up of patients with pre-capillary PH. A normal ventilation/perfusion scintigram virtually rules out CTEPH [53–56], with few

exceptions [57], while in established pre-capillary PH the presence of one or more mismatched segmental or larger perfusion defects generally indicates CTEPH [55]. In clinical practice, an abnormal perfusion study alone is diagnostic for CTEPH, if pulmonary parenchymal disease is absent.

### Pulmonary angiography

Pulmonary angiography is the established gold standard for CTEPH diagnosis and mandatory in the diagnostic work-up of affected patients. Allowing for the visualisation of thromboembolic obstructions, pulmonary angiography is the key data source for the assessment of operability [58, 59]. Major drawbacks of this technique are its invasive nature and limited availability, which results in limited expertise, especially in low-volume centres. Expert centre-specific experience with other imaging modalities (*e.g.* magnetic resonance) may obviate the need for invasive angiography in selected cases.

### Ancillary diagnostic tools

Recently, SCHEIDL *et al.* [60] demonstrated that capillary to end-tidal carbon dioxide gradients may be helpful in the differentiation between CTEPH and non-thromboembolic PH. In a retrospective analysis of 16 CTEPH and 21 PAH patients, capillary to end-tidal carbon dioxide gradients were significantly increased in CTEPH compared with PAH, at rest and during exercise. Of course, this study is limited by its retrospective nature and small size.

Intravascular optical coherence tomography (OCT) is a catheter-based modality that acquires images at a resolution of less than 10 μm, enabling visualisation of blood vessel wall microstructure *in vivo* at a high level of detail. The technique has been widely used in patients with coronary artery disease [61]. In a very recent report from Japan, OCT was used to guide percutaneous transluminal pulmonary angioplasty in patients with CTEPH [62].

## Treatment

PEA is the treatment of choice in patients with confirmed CTEPH. After successful PEA, patients are considered cured, since a vast majority nearly normalise their haemodynamic parameters and exercise capacity [63–65]. Surgical success not only depends on patient suitability, but also on the experience of the surgical team and available resources. PEA suitability is multifaceted, varies from centre to centre and cannot be based on uniform criteria [48].

A key issue in the pre-operative assessment of CTEPH patients is the degree of concomitant small-vessel arteriopathy and its contribution to PVR. Overall, patients with thromboembolic obstructions in the main, lobar or proximal segmental pulmonary arteries represent the target population for PEA, while those with more distal obstructions, or even lacking visible thromboembolic obstructions, are thought to be poor candidates for surgery [66]. Other criteria for PEA, except surgical accessibility of thrombi in the main, lobar or segmental pulmonary arteries, are a confirmed diagnosis of CTEPH in New York Heart Association (NYHA) functional class II–IV, a pre-operative PVR greater than 300 dyn·s·cm$^{-5}$, absence of severe comorbidities and patient consent [65].

In a contemporary registry [6], 63.3% of patients were considered operable and 36.7% inoperable. Inoperability was due to surgical inaccessibility of the occlusions in almost half of patients, imbalance between PVR and the amount of accessible occlusions in 10.1%, PVR greater than 1,500 dyn·s·cm$^{-5}$ in 2.5%, advanced age in 2.0%, comorbidities in 13.4% and other reasons in 22.7% of patients.

In fact, patients who do not undergo surgery or suffer from persistent or recurrent PH after PEA face an adverse outcome. In a vast majority of cases, out-of-proportion small-vessel arteriopathy that is indistinguishable from histological changes found in PAH lungs precludes affected

individuals from surgical therapy. Despite a strong rationale to administer vasodilator drugs in affected patients, current evidence from randomised controlled trials does not support the use of PAH-targeted pharmacotherapy. Still, compassionate use may be justified in cases considered inoperable, as a therapeutic bridge to PEA, in patients with persistent or recurrent PH after PEA, or even when surgery is contra-indicated due to comorbid conditions. Supportive medical treatment used for CTEPH patients includes oral anticoagulants, diuretics, digitalis and oxygen supplementation. Oral anticoagulants reduce the risk of recurrent thromboembolic events and lifelong anticoagulation is recommended [47].

## Pulmonary endarterectomy

PEA in CTEPH has not been assessed in randomised controlled trials, which are considered unethical in the absence of adequate alternative treatments. However, the outcome after successful PEA with respect to survival, functional status, haemodynamic parameters, RV function and pulmonary gas exchange is favourable for most patients [53, 67–70].

In a contemporary European registry comprising 386 PEA cases [48], in-hospital mortality due to peri-operative complications was as low as 4.7%. In patients evaluated within 1 year after surgery, median PVR had decreased from 698 to 235 dyn·s·cm$^{-5}$ and median 6-minute walking distance (6MWD) had increased from 362 to 459 m. NYHA functional class had improved in most patients, progressing from class III–IV to class I–II. Interestingly, PVR at the end of intensive care was an independent predictor of in-hospital death and death at 1 year. The 6MWD at diagnosis was also an independent predictor of death at 1 year. Survivors had a higher 6MWD and a lower PVR at diagnosis than non-survivors. Mortality rates, in-hospital and at 1 year, increased with increasing values of PVR at diagnosis to reach 10.6% and 12.8%, respectively, for those patients with a PVR exceeding 1,200 dyn·s·cm$^{-5}$. Moreover, the mortality rate tended to be higher in patients without a history of pulmonary embolism, it increased with increasing NYHA functional class at diagnosis and with duration of circulatory arrest. Centre expertise defined by number of PEAs performed per year tended to confer a lower risk for mortality after PEA [71, 72]. Single-centre experience reports survival rates of 90.3% at 5 years if a post-operative mean $P_{pa}$ under 30 mmHg is achieved [73].

## Medical treatment

So far, only one double-blind, randomised, placebo-controlled, adequately powered vasodilator trial has been completed in patients with inoperable CTEPH: the BENEFiT study investigated bosentan effects in inoperable CTEPH [7]. A total of 157 patients were enrolled and randomised in a 1:1 fashion to receive bosentan or placebo for 16 weeks. Patients could only be included if CTEPH had been judged inoperable because of surgically inaccessible thrombotic material, or persistence/recurrence of PH after PEA in the absence of recurrent thromboembolism. PVR, which directly reflects disease pathology, and the 6-minute walk test (6MWT), a measure of exercise capacity, were chosen as co-primary end-points. Although a significant treatment effect of bosentan over placebo on PVR (-24.1% of baseline, 95% CI -31.5- -16.0%) could be demonstrated, there was only a minor effect on the second co-primary end-point (6MWD +2.2 m, 95% CI -22.5– +28.8 m).

A subgroup of patients enrolled in the AIR (Aerosolized Iloprost Randomized) study, a prospective, randomised, placebo-controlled trial, suffered from CTEPH [74]. The study failed to demonstrate beneficial effects of inhaled iloprost in this population.

Despite disappointing study results, a significant proportion of real-world CTEPH patients are on specific vasodilator treatment. Of the 679 patients studied in the European prospective registry [6], 37.9% initiated at least one PAH-targeted therapy (28.3% of operable and 53.8% of inoperable patients), including phosphodiesterase type-5 inhibitors (PDE-5 I), ERAs and prostacyclin analogues. Cautious use of PAH-targeted therapies is, however, endorsed by current guidelines [75], since

pre-operative treatment may induce unnecessary delay to a potentially curative surgical intervention [48, 76].

In the near future, patients may benefit from adaptive trial designs and new vasodilator compounds. Currently, the effects of vasodilators, such as riociguat (CHEST trial) [77] and treprostinil sodium (CTREPH trial), are being tested in a multi-national, placebo-controlled, randomised fashion.

## Future perspectives

Successful PEA is still the only curative therapy for patients with CTEPH and will remain the treatment of choice. However, the assessment and quantification of concomitant small-vessel arteriopathy that may preclude an adequate relief from PH after PEA in 10–20% of patients, and increased operative mortality remains a black box in the diagnostic work-up of CTEPH patients. Innovative techniques for the evaluation of the distal pulmonary vascular bed have been introduced. One of the future efforts to be undertaken is the establishment of standardised approaches with clear-cut differentiation between surgical candidates and those who are not suitable for surgery. Recent reports of successful percutaneous transluminal pulmonary angioplasty [63] may widen therapeutic opportunities possibly even further with the availability of drug-eluting balloons, and even set the stage for staged hybrid procedures with adjuvant medical therapy.

At present, none of the vasodilator compounds approved for the treatment of nonthromboembolic PH have proven effective in inoperable CTEPH. Despite its outcome, the BENEFiT trial reinforced the principle of vasodilation as a future direction in CTEPH research.

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# Chapter 10

# Pulmonary hypertension associated with left heart disease

*Yochai Adir** and Offer Amir*#

**SUMMARY: Left heart disease (LHD) is probably the most frequent cause of pulmonary hypertension (PH). Although in the past, rheumatic mitral valve stenosis has been the most common cause of this condition, PH-LHD mainly results from heart failure related to systolic and/or diastolic dysfunction of the left ventricle (LV) and is associated with elevated left-sided cardiac filling pressures. Most patients have a passive increase in pulmonary arterial pressure ($P$pa) due to backward transmission of the elevated left atrial pressure, while a small subset develop severe PH with elevated transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR). When present, PH is usually associated with a poor prognosis and increased mortality. Optimising heart failure regimens and corrective valve surgery are the cornerstones of the treatment of PH in LHD. Although PH-LHD may evolve to right ventricular (RV) failure and is associated with some changes in the pulmonary vascular bed similar to pulmonary arterial hypertension (PAH), there are no data to support the use of PAH-specific therapies in the setting of PH-LHD. However, recent studies have suggested the usefulness of sildenafil, a phosphodiesterase type-5 inhibitor (PDE-5 I). This chapter addresses the epidemiology, pathophysiology, risk factors and treatment controversies of PH-LHD.**

**KEYWORDS: Heart failure, left heart disease, pulmonary hypertension, valvular disease**

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Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure ($P$pa) $\geqslant$25 mmHg at rest as assessed by right heart catheterisation (RHC) [1, 2]. The clinical classification of PH includes heterogeneous conditions with different clinical presentations, pathophysiology and management [1, 2]. The first category, termed pulmonary arterial hypertension (PAH), is characterised by the presence of pre-capillary PH in the absence of other causes of the pre-capillary PH. PAH includes a group of rare diseases characterised by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular (RV) failure and premature death [1, 2]. With

minimal prevalence and incidence of 15 cases per million and 2.4 cases per million per year, respectively, PAH is clearly a rare disease. The second clinical classification includes patients with PH secondary to elevated left-sided cardiac filling pressures due to left heart disease (LHD), as assessed by pulmonary capillary wedge pressure ($P_{pcw}$) or left ventricular (LV) end-diastolic pressure. These patients are classified according to the Dana Point classification as World Health Organization (WHO) group 2, PH due to PH-LHD, which is the most common form of PH (table 1) [1, 2]. Furthermore, pulmonary complications of acute and/or chronic increases in LV filling pressure are a primary cause of increased morbidity and mortality in patients with a failing heart [3, 4]. PH-LHD can result from any of a number of left-sided valvular or myocardial diseases [5–7]. Although in the past, rheumatic mitral valve stenosis has been the most common cause of this condition, PH-LHD most commonly results from heart failure related to systolic and/or diastolic dysfunction of the LV [5–7]. The prevalence of PH-LHD reported in the literature varies greatly, depending on the severity of LV dysfunction and the definition of PH. Heart failure with preserved ejection fraction (HFPEF) is increasingly recognised as the predominant cause of PH-LHD [7, 8], and was recently reported by the Dana Point updates to be the most frequent cause of PH-LHD [9].

The pathophysiology, haemodynamic characteristics, clinical presentation and treatment options of PH-LHD are reviewed in this chapter.

# Pathophysiology

## Pathological changes

Increased pulmonary venous pressure may lead to functional and structural changes in the pulmonary circulation. The earlier changes are seen in the alveolocapillary membrane. Previous studies reported increased capillary endothelial basement membrane thickness due to excessive deposition of type IV collagen in lung biopsies from patients with pulmonary venous hypertension secondary to heart failure or mitral stenosis [10–12].

Increased lung interstitial connective tissue in conjunction with increased production of extracellular matrix components raise extravascular fluid storage capacity and serve as a compensatory mechanism to eliminate alveolar oedema [13].

Increased venous pressure with disruption of the endothelium may cause activation of vascular serine elastase and matrix metalloproteinases; these, together with release of growth factors, lead to smooth muscle growth and migration and elastin synthesis, which promote hypertrophy with fibrous changes. Lung biopsies in these patients exhibit enlarged and thickened pulmonary veins, pulmonary capillary dilatation, alveolar haemorrhage, and lymphatic vessel and lymph node enlargement [14]. Distal pulmonary arteries may be affected by medial hypertrophy and intimal fibrosis, explaining the so-called "reactive" component of the elevated pulmonary pressures [14, 15]. Importantly, plexiform lesions are not seen in patients with PH-LHD.

**Table 1.** Haemodynamic definition of pulmonary hypertension (PH) secondary to left heart disease (LHD)

| Definition | Characteristics |
|---|---|
| **PH** | Mean $P_{pa}$ ⩾25 mmHg |
| **Post-capillary PH**[#] | Mean $P_{pa}$ ⩾25 mmHg<br>$P_{pcw}$ >15 mmHg |
| **Passive** | TPG ⩽12 mmHg |
| **Out-of-proportion (reactive)** | TPG >12 mmHg |

$P_{pa}$: pulmonary artery pressure; $P_{pcw}$: pulmonary capillary wedge pressure; TPG: transpulmonary gradient. [#]: PH-LHD group 2.

Interestingly, these changes are not uniform in all patients with increased pulmonary venous pressure, accounting for the different haemodynamic patterns and suggesting a genetic predisposition in patients with prominent morphological changes [6, 16].

## Endothelial dysfunction

In the pulmonary vasculature, as in the systemic circulation, the endothelium plays a central role in the local

control of tone through the regulated release of nitric oxide (NO) and endothelin [17]. Indeed, the importance of endothelium-derived NO in determining the basal pulmonary vascular tone was reported in previous studies [17]. Both animal and human studies suggested that NO-dependent pulmonary vasodilatation is impaired in heart failure. PORTER *et al.* [18], using intravascular ultrasound, found that intrapulmonary infusion of acetylcholine caused vasoconstriction, which was accentuated by inhibition of guanylate cyclase in patients with heart failure and normal $P_{pa}$, but failed to cause vasodilatation in patients with heart failure and PH. COOPER *et al.* [19] demonstrated that the vasoconstriction response to $N^G$-mono-methyl-L-arginine (L-NMMA), an analogue of L-arginine that inhibits NO synthase, was attenuated in patients with heart failure and PH. These and other findings suggest that the loss of NO-dependent vasodilatation may contribute to the development of PH.

Endothelin is a potent arterial and venous vasoconstrictor peptide that is stored in the pulmonary epithelium and both produced and cleared by the lungs [20]. Endothelin might also induce proliferation and hypertrophy of smooth muscle, and increase collagen synthesis, contributing to pulmonary vascular remodelling [21]. Elevated plasma endothelin (ET)-1 levels were found in patients with heart failure, and a direct correlation between $P_{pa}$ and circulating ET-1 levels was reported [22, 23]. Plasma ET-1 levels increased significantly in heart failure patients from the pulmonary artery to the capillary wedge region, with a consequent net pulmonary ET-1 production that is also proportional to PVR [24]. ET-1 mediates its effects through two types of receptors: $ET_A$, which promotes vasoconstriction and cellular growth; and $ET_B$, which mediates ET-1 clearance. $ET_B$ receptors were reduced in patients with heart failure, while $ET_A$ was upregulated, explaining the elevated ET-1 blood levels and the enhanced vasoconstriction [25, 26].

## Haemodynamics

It is well known that elevated left-sided filling pressures can generate PH by passive or reactive mechanisms; however, the risk factors for this mechanism are not known, and it is not possible to predict which patients will develop PH and to what degree.

### Passive PH

Most patients will have a passive increase in $P_{pa}$ due to the backward transmission of the elevated left atrial pressure necessary to overcome the increased downstream resistance. The necessity for the RV to generate high systolic pressures to ensure adequate cardiac output results in moderate degrees of PH. In such a case, RHC will disclose elevated $P_{pcw}$ and mean $P_{pa}$, with minimal increase in transpulmonary gradient (TPG; defined as mean $P_{pa}$ minus $P_{pcw}$, normal values $\leqslant$12 mmHg), and, usually, normal PVR [1, 2]. Interventions that normalise the $P_{pcw}$, such as diuretic therapy, would also be expected to normalise the $P_{pa}$. This is generally referred to as reversible PH and it is presumed that there are no demonstrable abnormalities in the pulmonary arterial bed [1, 2, 6, 7]. Indeed, a study that evaluated 1,000 patients with advanced heart failure for heart transplantation found that the systolic $P_{pa}$ ($sP_{pa}$) was closely correlated with $P_{pcw}$, and the reduction in $sP_{pa}$ during therapy was strongly determined by $P_{pcw}$ reduction [27]. The same authors also reported that in patients with HFPEF, right-sided filling pressures often reflect left-sided filling pressures [28]. Other studies in patients with mitral stenosis and PH have shown that removing the mitral valve gradient, either surgically or with percutaneous balloon valvuloplasty, results in normalisation of the $P_{pa}$ [29–31].

### Reactive PH

In a second, smaller group of patients, the PH is the result of functional and/or structural abnormalities of the pulmonary vascular bed, caused by the chronically elevated $P_{pcw}$, as discussed earlier in the Pathological changes section [15, 17]. These patients will have increased mean $P_{pa}$, TPG ($>$12 mmHg) and PVR; and, in contrast to the passive form, lowering the $P_{pcw}$ to normal may not

normalise the $P_{pa}$ [1, 2, 32]. These patients can develop severe PH, also termed reactive or out-of-proportion PH [1, 2, 6, 7]. Interestingly, several studies of the haemodynamic characteristics of patients with heart failure and out-of-proportion PH reported a severe increase in s$P_{pa}$ and only a mild increase in diastolic $P_{pa}$, and a low diastolic $P_{pa}$–$P_{pcw}$ gradient ($\leqslant$5 mmHg) [33, 34]. It seems that the diastolic $P_{pa}$–$P_{pcw}$ gradient ($\geqslant$10 mmHg) can differentiate between passive and reactive increases in $P_{pa}$, an approach proposed in the past that should be considered part of the definition of out-of-proportion PH in order to avoid the marked flow and pressure dependency of the TPG [35, 36]. It is important to emphasise that the development of out-of-proportion PH is probably not closely related to the severity of heart failure, since severe PH was reported in patients with mild LV dysfunction and only mildly elevated $P_{pcw}$.

## Challenge and vasoreactivity testing

Interestingly, borderline $P_{pcw}$ at rest may be found on RHC in patients with heart failure, in particular if diuretics are used. In this scenario, an exercise test, or fluid or inotropic challenge at the time of RHC may induce an increase of $P_{pcw}$, helping to differentiate between idiopathic pulmonary arterial hypertension (IPAH) and HFPEF with out-of-proportion PH (HFPEF-PH) [37–40]. However, there is no consensus on specific protocols for either exercise or fluid challenge, and normal age-related $P_{pcw}$ values are not available in these settings.

Acute vasoreactivity test during RHC is recommended in patients with out-of-proportion PH, particularly in candidates for heart transplantation [32, 41]. Various drugs have been used to assess acute vasoreactivity in PH-LHD, including intravenous sodium nitroprusside, prostacyclin and inhaled NO (table 2). The objective is to see whether the PH is reversible, as evidenced by reduction of the TPG and PVR during drug administration, without raising $P_{pcw}$ or lowering cardiac output, or causing systemic hypotension. However, there is no standard definition of a responder in patients with PH-LHD. Inhaled NO testing in heart failure leads to a reduction of PVR that is attributable to an increase in $P_{pcw}$ with no change in cardiac output, whereas the use of nitroprusside is limited by systemic hypotension (table 2) [41].

## Exercise-induced PH

Exercise-induced PH is common in patients with both reduced as well as preserved LV ejection fraction (LVEF) [42]. It is considered an important cause of exertional dyspnoea and exercise intolerance. In patients with heart failure and normal $P_{pa}$ at rest, $P_{pcw}$ elevation in response to mild exercise, in concert with an abnormal pulmonary vascular response, failing to appropriately decrease PVR relative to the increase of cardiac output leads to increased $P_{pa}$ [42–45]. HA *et al.* [42] reported that exercise-induced PH is common in subjects with HFPEF and that it is strongly associated with tricuspid regurgitant jet velocity (TRJV), age and increase in LV filling pressure, estimated by the ratio between early and later ventricular filling ratio (E/Ea). SHIM *et al.* [43] found that patients with HFPEF who had exercise-induced PH in the presence of elevated the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e′) had a higher rate of hospitalisation or mortality. These studies suggest that exercise-induced PH is an early, mild and clinically relevant phase of PH, and screening and early intervention for exercise-induced PH may be indicated

**Table 2.** The haemodynamic effects of the most commonly used agents for pulmonary vasoreactivity tests in patients with heart failure

| Drug | Dose | PVR | TPG | $P_{pcw}$ | SBP |
|---|---|---|---|---|---|
| **Intravenous nitroprusside** | 250–750 μg·kg$^{-1}$·min$^{-1}$ | ↓ | ↓ | - | ↓ |
| **Intravenous epoprostenol** | 2–10 ng·kg$^{-1}$·min$^{-1}$ | ↓ | ↓ | - | ↓ |
| **Inhaled NO** | 10–40 ppm | ↓ | ↓ | -/↑ | - |

PVR: pulmonary vascular resistance; TPG: transpulmonary gradient; $P_{pcw}$: pulmonary capillary wedge pressure; SBP: systemic blood pressure; NO: nitric oxide. ↓: reduction; -: no effect; ↑: increase.

[42–45]. Exercise-induced PH is not specific to heart failure. Elite athletes show a higher increase in $P_{pa}$ in response to exercise because of a larger increase in stroke volume, and patients with PAH may also have exaggerated responses to exercise with marked increases in $P_{pa}$. Therefore, the assessment of pulmonary pressures under conditions of exercise remains an area of controversy, mainly because of the lack of standardised data and the lack of a concept by which to categorise an abnormal response. One consensus appears to be that mean $P_{pa}$ during submaximal exercise should be measured in the context of flow.

## Epidemiology and risk factors

Heart failure is largely a disease of old age and represents the leading hospital diagnosis in older adults [46, 47]. It has been estimated that there are currently over 6.5 million heart failure patients in Europe and over 5 million in the USA; more than 550,000 new cases are diagnosed annually in the USA [46, 47]. Approximately two-thirds of cases are secondary to systolic dysfunction and about one-third are secondary to diastolic dysfunction [46, 47]. However, the prevalence of HFPEF is increasing with age, approaching 50% in patients over 70 years old [48].

PH is present in about two-thirds of patients with severe heart failure and reduced LVEF, which is commonly associated with RV dysfunction [32, 39, 49].

The prevalence of PH in HFPEF has not been established. KLAPHOLZ *et al.* [50] reported a mean $\pm$SD $sP_{pa}$ of 47 $\pm$ 17 mmHg in 44% of 272 patients hospitalised for exacerbation of HFPEF diagnosed by echocardiography. A community-based study of 244 patients with HFPEF (age 76 $\pm$ 13 years; 45% males) reported that PH was highly prevalent (83%), often severe (median $sP_{pa}$ of 48 mmHg, measured by echocardiography) and strongly predicted mortality [51]. The development of PH in this study was related to the extent of pulmonary venous hypertension as estimated by Doppler indexes. However, after accounting for this passive component of PH, the severity of PH suggests that some cases may have been affected by out-of-proportion PH [51]. A retrospective analysis of 477 consecutive echocardiographic studies in subjects with HFPEF demonstrated an association between the severity and grade of diastolic dysfunction and estimated $P_{pa}$ [52].

Compared with patients with HF and reduced LVEF, where coronary artery disease and primary cardiomyopathy are the most common causes, those with HFPEF are typically older and more likely to be female, and have a higher likelihood of having hypertension (prevalence up to 88%), obesity (prevalence of body mass index (BMI) $>30$ kg·m$^{-2}$, approximately 40%) and atrial fibrillation [53–55]. In conjunction, the prevalence of diabetes (about 30%) and coronary artery disease (40–50% of patients with HFPEF) is substantial, being similar to that in patients with heart failure and reduced LVEF [54]. Individuals with metabolic syndrome and normal LV systolic function frequently show abnormalities in LV diastolic function (*i.e.* impaired relaxation). These findings are also evident in subjects with only one or two metabolic syndrome criteria (or pre-metabolic syndrome), and components of the metabolic syndrome such as hypertension and obesity are independent predictors of the development of HFPEF [56–58]. Whether the presence of metabolic syndrome also confers increased risk for PH is unknown, although it is plausible. ROBBINS *et al.* [58] described 17 patients (77% female) with HFPEF-PH who had two or more components of metabolic syndrome. According to recent studies, patients with HFPEF-PH are older, mostly females, and have a higher prevalence of cardiovascular features of metabolic syndrome (obesity, diabetes, hypertension and ischaemic heart disease) and atrial arrhythmia [33, 34]. THENAPPAN *et al.* [34] compared the clinical, echocardiographic and haemodynamic features of patients with HFPEF-PH (n=100), PAH (n=522) and HFPEF without pulmonary vascular disease (n=45). Compared with patients with PAH, those with HFPEF-PH were older, had a higher prevalence of cardiovascular comorbidities, worse exercise capacity and renal function, more frequent left atrial enlargement and less frequent right atrial enlargement. PH was less severe in HFPEF-PH patients than in PAH patients. Compared with HFPEF patients without PH, HFPEF-PH patients were often female and more symptomatic, more often had RV hypertrophy and right atrial enlargement, and had higher right atrial pressure ($P_{ra}$).

Systemic hypertension and peripheral vascular stiffness are known independent risk factors for the development of HFPEF [48, 59]. Furthermore, recent studies have demonstrated that metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness [59]. Vascular stiffness, in turn, may contribute to the development of HFPEF and may also directly involve the pulmonary vasculature, leading to increased PVR and $P_{pa}$. A recent study demonstrated that unlike the systemic circulation, pulmonary vascular resistance and compliance display a highly predictable, inverse correlation [60]. The consistent relationship between PVR and pulmonary vascular compliance allows the prediction of the decline of PVR required by a given treatment to adequately lower pulmonary vascular compliance and, thus, reduce pulsatile and net RV afterload. The PVR–pulmonary vascular compliance relationship was found to be sensitive to changes in pulmonary venous pressure (mean $P_{pcw}$) because elevation of this pressure lowers pulmonary vascular compliance for any given PVR, augmenting RV pulsatile afterload. Furthermore, in patients with HFPEF with a marked rise in $P_{pcw}$ during exercise, a disproportionate decline in pulmonary vascular compliance and increased pulsatile load was found. This identifies a novel mechanism whereby left-side diastolic dysfunction contributes to RV load [60].

Development of PH in association with valvular dysfunction has been shown to be a marker of severity. PH frequently complicates mitral stenosis and may significantly influence long-term prognosis [29–31, 36]. The increase in $P_{pa}$ may be out of proportion with the degree of left atrial pressure increase, reflecting an increase in PVR. Elevation of PVR is an important pathophysiological event in mitral stenosis, and the level of $P_{pa}$ is an indicator of surgical risk. Interestingly, there is a subset of mildly symptomatic patients with severe mitral stenosis and severe PH who are usually young, with preserved sinus rhythm [61, 62].

PH can also occur in patients with mitral regurgitation. The evolution of PH in these patients is not necessarily related to the LV dysfunction that complicates advanced stages of mitral regurgitation, and may occur in patients with chronic, isolated mitral regurgitation with normal LV function [63].

PH in the setting of aortic valve stenosis and/or regurgitation is less common than in mitral valve disease. SILVER *et al.* [64] performed RHC in 45 patients with aortic stenosis and found PH, defined as $sP_{pa}$ >50 mmHg, in 13 (29%) of them. Patients with aortic stenosis and PH had a higher incidence of congestive heart failure, a lower LVEF and cardiac index, and more mitral regurgitation compared with patients with aortic stenosis and normal $P_{pa}$. Eight of the 13 patients had a TPG $\geqslant$10 mmHg, suggesting a "fixed" component of the elevated pulmonary pressures. In another study, the incidence of PH ($sP_{pa}$ $\geqslant$60 mmHg) in 139 patients with severe aortic regurgitation was reported to be 24% [65]; all had high left-sided filling pressures, suggesting that PH was a consequence of severe, long-standing regurgitation with ventricular dysfunction.

## Diagnosis

The clinical manifestations of PH-LHD do not differ significantly from those of PAH; both exhibit dyspnoea on exercise and, eventually, overt RV failure and peripheral oedema. Important and distinctive symptoms of PH-LHD not shared by PAH are orthopnoea and paroxysmal nocturnal dyspnoea [66, 67].

Effort dyspnoea is the most common symptom of PH-LHD. In patients with chronic LV failure, LV function at rest is poorly correlated with exercise capacity. During exercise, systemic vascular resistance (SVR) falls while PVR remains elevated, leading eventually to overt RV failure and peripheral oedema; in addition, there is an inverse relationship between peak oxygen uptake ($V'O_2$) and resting $P_{pa}$ or PVR, as opposed to a positive correlation between RV ejection fraction at rest and exercise to peak $V'O_2$. These findings suggest that increasing RV afterload during exercise is responsible for the reduced exercise capacity [39, 41, 68, 69].

Patients with HFPEF and normal $P_{pa}$ at rest often exhibit $P_{pcw}$ elevation in response to mild exercise, which may result in increased $P_{pa}$. This may be due to failure of an associated abnormal pulmonary vascular response to appropriately decrease PVR relative to the increase of cardiac

output. These patients probably have worse outcomes and a higher rate of hospitalisation and mortality than those without exercise-induced PH [43, 45].

An ECG in these patients may show evidence of old myocardial infarction, left atrial enlargement and LV hypertrophy. Chest radiography may show signs of pulmonary congestion with redistribution of pulmonary vessels, cardiomegaly, Kerley B lines and pleural effusion. Computed tomography (CT) of the chest may reveal a mosaic perfusion pattern with diffuse ground-glass opacities.

Echocardiography plays a critical diagnostic role in patients with heart failure, in part because the physical examination, ECG and chest radiograph do not provide information that distinguishes diastolic from systolic heart failure [70]. Furthermore, echocardiography identifies valvular dysfunction and assesses its severity [70]. In patients with preserved ejection fraction, the presence of a dilated left atrium, abnormal Doppler estimates of mitral and pulmonary venous flow velocity, and abnormal mitral tissue Doppler velocities suggest HFPEF [33, 51]. The ratio of early mitral flow velocity (E) to early mitral tissue Doppler velocity (E1) was found to correlate with left atrial pressure, and an E/E1 ratio $>15$ was almost invariably associated with a mean left atrial pressure $>15$ mmHg [71]. Despite the evidence documented by echocardiography, RHC with measurement of $P_{pcw}$ and/or LV end-diastolic pressure remains the gold standard for diagnosis of heart failure and assessment of PH [72].

## Prognosis

When present, PH is usually associated with a poor prognosis in patients with LHD.

Elevated $P_{pa}$ and abnormal RV function are important determinants of exercise capacity and prognosis in patients with heart failure and reduced LVEF, and the mortality associated with biventricular failure is more than two-fold higher compared with isolated LV failure [40, 68, 69, 73–78]. In the advanced stages, when RV failure complicates the course of heart failure and reduced LVEF, patients have severe tricuspid regurgitation secondary to annular dilatation, with increased jugular venous pulse, chronic liver congestion, ascites and peripheral oedema. GHIO *et al.* [49] followed 377 patients with moderate-to-severe heart failure (ejection fraction $<35\%$) for a median of 17 months following RHC and found that those with PH and reduced RV function had the worst prognosis and survival among patients with advanced heart failure and reduced LVEF. The prognosis in patients with normal RV function and PH was similar to that in patients with normal $P_{pa}$. In contrast, when $P_{pa}$ was normal, reduced RV function did not carry an additional risk. However, another study found that RV dysfunction is more common in patients with dilated cardiomyopathy compared with patients with ischaemic cardiomyopathy (65% *versus* 16%), although the mean $P_{pa}$ was the same in both groups, suggesting that the impact of PH *per se* on the prognosis is difficult to assess [73].

Severe PH is a contraindication for orthotopic cardiac transplantation since the RV of the implanted organ will fail acutely due to the high PVR, resulting in allograft failure and death. The risk was shown to be directly proportional to both PVR and TPG [79–82].

BUTLER *et al.* [39] studied 182 patients with baseline normal pulmonary pressures or reversible PH, defined as a decrease in PVR to $\leqslant 2.5$ Wood units, who underwent heart transplantation. Those with systolic $P_{pa}$ $>50$ mmHg and TPG $\geqslant 16$ mmHg had a higher risk of mortality, suggesting that pre-transplant PH, even when reversible to a PVR of $\leqslant 2.5$ Wood units, is associated with a higher mortality post-transplant. Specific values of PVR and TPG have been proposed as risk predictors. Heart failure patients with a TPG $<12$ mmHg or PVR $<3$ Wood units are considered suitable with an acceptable risk in most transplant centres, whereas patients with a TPG $\geqslant 15$ mmHg or PVR $\geqslant 5$ Wood units, despite acute reversibility testing, are considered unsuitable candidates [83–88]. Following a successful transplantation in patients with mild-to-moderate PH, $P_{pa}$ values tend to normalise over a 6–12-month period. The greater the PH level prior to surgery, the longer the time to resolution. In some patients, an incomplete resolution may be observed, with residual elevations in $P_{pa}$ and PVR [89, 90].

The prognosis for patients with HFPEF-PH is not well defined. However, recent studies suggested that PH, evaluated by echocardiography, has a negative impact on mortality. LAM *et al.* [51] reported that s$P_{pa}$ >35 mmHg was strongly associated with mortality, and KJAERGAARD *et al.* [91] found that the presence of PH increased short- and long-term mortality in patients with HFPEF.

In patients with valvular heart disease, PH increased the likelihood of poor surgical outcomes. However, surgery in these patients is still associated with better outcomes compared with conservative management [62–65, 92].

## Treatment

In patients with HF, reduced LVEF and PH, the traditional therapies for heart failure of diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and β-blockers may result in reduction of the $P_{pa}$ [93–95]. However, if the patient remains significantly symptomatic despite these measures and moderate-to-severe PH persists, RHC may be indicated to clarify the haemodynamic details. A search for other causes of PH should also be undertaken, such as ventilation/perfusion scanning and polysomnography.

There is no evidence-based treatment for patients with HFPEF and there are no data on the therapeutic approach to patients complicated by PH. Treatment of HFPEF is linked primarily to the underlying aetiology [48, 96–98]. Aggressive management of systemic hypertension should be instituted, especially in patients with LV hypertrophy and diabetes mellitus [96–98]. The cornerstones of therapy include sodium restriction and judicious use of diuretics and nitrates to relieve symptoms of congestion, together with drugs that slow the heart rate and improve diastolic filling time, such as β-blockers and calcium channel blockers (CCBs) [96–98]. Several recent studies demonstrated that angiotensin receptor antagonists improve exercise tolerance in this setting [99, 100]. The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Preserved trial suggested that treatment with candesartan reduces hospitalisation related to diastolic heart failure, although there was no effect on mortality [100].

Even when the left atrial pressures are normalised, a proportion of these patients are left with significant PH. Whether modification of the features of the metabolic syndrome, such as dietary control, weight reduction and blood pressure control, will result in an improvement of symptoms and $P_{pa}$ in patients with HFPEF remains an open question and worth investigation.

There are no clear indications for additional therapeutic measures in patients with out-of-proportion PH other than optimising traditional therapy for heart failure. In fact, there is no evidence that the drugs approved for PAH are effective and safe in this setting. The main concern is that by decreasing the PVR, the consequent increase in venous return to the LV may further increase the already elevated left heart filling pressure, resulting in deterioration rather than improvement. Early experiences with PAH-specific treatments in the setting of LV failure were disappointing. The major clinical studies assessing vasodilators in the treatment of PAH in patients with heart failure are summarised in table 3.

### Prostacyclins

SUETA *et al.* [101] studied the acute and prolonged effects (12 weeks) of continuous *i.v.* epoprostenol on 33 patients with severe heart failure: the drug resulted in significant reductions in mean $P_{pa}$, PVR and $P_{pcw}$, and a marked increase in cardiac output. These beneficial haemodynamic effects persisted with long-term infusions. Based on this and other studies that suggested clinical benefit of *i.v.* epoprostenol [101, 113], a large randomised controlled study (Flolan International Randomized Survival Trial; FIRST) was initiated [102]. The FIRST study randomised 471 patients with advanced heart failure to receive continuous epoprostenol infusion plus standard care or standard care alone. Although a haemodynamic improvement was seen acutely among patients receiving epoprostenol, evidenced by an increase in cardiac index and a decrease in $P_{pcw}$ and PVR, the study was terminated

early due to a strong trend toward increased mortality rates in patients on the drug. Based on the findings of this study, chronic use of epoprostenol in patients with systolic heart failure is considered contraindicated. Explanations for the increase in mortality include sympathetic stimulation due to systemic vasodilatory effects and/or unknown detrimental effects of prostanoids in this setting [114]. The more recent data on the inhaled prostacyclin analogue iloprost indicate short-term beneficial effects in patients undergoing assessment for heart transplantation, with improvements recorded in mean $P_{pa}$, PVR and $P_{pcw}$ during vasoreactivity testing, but these findings must be considered with caution [115].

### Endothelin receptors antagonist

Plasma levels of endothelin have been shown to be elevated in heart failure, to correlate with the severity of heart failure and may contribute to the excessive systemic and pulmonary vasoconstriction that exists in the disease [116–118]. In animal models of heart failure, treatment with both selective and nonselective endothelin receptor antagonists (ERAs) prevented LV remodelling and improved exercise capacity [119, 120].

Studies on the short-term haemodynamic effect of ERAs in patients with chronic heart failure were initially encouraging [103, 121, 122]. A randomised, placebo-controlled study evaluating the haemodynamic effects of 6-hour infusions of tezosentan compared with placebo in 61 patients with New York Heart Association (NYHA) functional class III–IV heart failure demonstrated increased cardiac index with reduction in $P_{pcw}$ PVR and SVR [121]. Similar results were reported in a larger study of patients admitted to hospital and in need of *i.v.* treatment for acute heart failure [103]. A short-term study evaluating 2 weeks of the nonselective ERA bosentan in 36 patients with symptomatic heart failure, despite treatment with standard regimen, resulted in a reduction of both systemic and pulmonary pressures, and an increase in cardiac output [122]. These encouraging results prompted long-term randomised trials. In the REACH-1 (Research on Endothelin Antagonists in Chronic Heart Failure) study, 370 patients with advanced heart failure (NYHA functional class IIIB–IV) received bosentan or placebo and were followed for up to 26 weeks [104]. The target dose of bosentan was 500 mg twice a day, which is much higher than the current recommended dose for PAH. The trial was stopped prematurely due to safety issues, namely elevated liver transaminases; the question of the possible long-term benefit of using lower doses was also raised based on a trend towards reduction in morbidity and mortality. A larger study, ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure), evaluated the effects of low-dose bosentan in patients with severe heart failure (LVEF <35%, NYHA functional class IIIB–IV) [105]. A total of 1,613 patients were randomised to receive either bosentan (125 mg twice a day) or placebo [105]. No improvement in outcome was demonstrated in either group. There was an increased risk of early heart failure exacerbations due to fluid retention in patients treated with bosentan. Other studies using selective $ET_A$ antagonists also failed to improve outcome, and showed a trend towards increased mortality and early exacerbation of heart failure [106, 107].

The reasons for the lack of efficacy of ERAs in heart failure are unclear; the small relevance of endothelin system activation in patients already treated with US Food and Drug Administration (FDA)-approved drugs for heart failure has been suggested [123].

## Phosphodiesterase type-5 inhibitors

Previous studies in animal models and in humans suggest that endothelial dysfunction is present in heart failure, with a relative deficiency in NO production [124, 125]. Inhaled NO administered to patients with heart failure lowers PVR, increases cardiac index and improves exercise capacity, without altering systemic arterial pressure, suggesting that phosphodiesterase type-5 (PDE-5) inhibition may reduce PVR and improve cardiac performance [126]. Recent studies reported that PDE-5 is also present in cardiac myocytes and PDE-5 inhibition resulted in antihypertrophic, anti-apoptotic and ischaemic pre-conditioning effects [127–132]. Acute administration of sildenafil in

**Table 3.** Major trials with pulmonary vasodilators in patients with heart failure

| First author [ref.] | Patient population | Treatment | Primary end-point | Findings and outcome |
|---|---|---|---|---|
| **SUETA [101]** | Advanced systolic heart failure, NYHA FC III–IV, n=33 | Continuous *i.v.* epoprostenol infusion for 12 weeks | 6MWD | Significantly improved 6MWD<br>Improved haemodynamics |
| **CALIFF [102]** | Advanced systolic heart failure, NYHA FC IIIB–IV, n=471 | Continuous *i.v.* epoprostenol | Survival | Early termination because of strong trend toward decreased survival in the patients treated with epoprostenol |
| **TORRE-AMIONE [103]** | Advanced systolic heart failure, NYHA FC III–IV, n=61 | 6-hour infusions of tezosentan at 5, 20, 50 and 100 mg·h$^{-1}$ | Safety and haemodynamic parameters | Tezosentan significantly decreased PVR and $P_{pcw}$, and significantly increased cardiac index |
| **PACKER [104]** | Advanced systolic heart failure, NYHA FC III–IV, n=371 | Bosentan 500 mg twice daily for 26 weeks | | Safety concerns led to early termination of the trial (liver toxicity) when only 174 patients completed 26 weeks of therapy<br>Bosentan-treated patients had an increased risk of heart failure during the first month of treatment but a decreased risk of heart failure during the fourth, fifth and sixth months of therapy |
| **The ENABLE study [105]** | Advanced systolic heart failure, NYHA FC IIIB–IV, n=1613 | Bosentan 125 mg twice daily for 1.5 years | All-cause mortality or hospitalisation for heart failure | Treatment with bosentan appeared to confer an early risk of worsening heart failure, necessitating hospitalisation as a consequence of fluid retention |
| **LÜSCHER [106]** | Advanced systolic heart failure NYHA FC III, n=157 | Darusentan 30, 100 or 300 mg daily for 3 weeks | Haemodynamic and neurohumoural effects | Cardiac index significantly increased but $P_{pcw}$, $P_{pa}$, PVR and $P_{ra}$ did not change<br>Heart rate, mean arterial pressure and plasma catecholamine levels remained unaltered, but SVR decreased significantly<br>Higher dosages were related to more adverse events (including death), particularly early exacerbation of congestive heart failure |
| **ANAND [107]** | Advanced systolic heart failure, NYHA FC II–IV, n=642 | Darusentan at 10, 25, 50, 100 or 300 mg daily for 24 weeks | Change in LVESV at 24 weeks from baseline, measured by MRI | Darusentan did not improve cardiac remodelling, clinical symptoms or outcomes |

**Table 3.** Continued

| First author [ref.] | Patient population | Treatment | Primary end-point | Findings and outcome |
|---|---|---|---|---|
| **GUAZZI [108]** | Advanced systolic heart failure, NYHA FC II–III, n=46 | Sildenafil 50 mg three times daily for 6 months | Assessments of endothelial function by brachial artery flow-mediated dilatation, cardiopulmonary exercise testing and ergoreflex response | Sildenafil improved exercise ventilation and aerobic efficiency |
| **LEWIS [109]** | Advanced systolic heart failure, NYHA FC II–IV with secondary PH, mean $P_{pa}$ >25 mmHg, n=13 | Sildenafil 25–75 mg three times daily for 3 months | Change in peak $V'_{O_2}$ from baseline | The change in peak $V'_{O_2}$ from baseline was greater in the sildenafil group<br>Sildenafil significantly reduced PVR and increased cardiac output with exercise without altering $P_{pcw}$ |
| **TEDFORD [110]** | Advanced heart failure, treatment with LV assist device implantation and persistent PH (defined as PVR >3 Wood units), n=58 | Sildenafil 25–75 mg orally three times daily for 3 months | Change in PVR | Sildenafil significantly reduced PVR and mean $P_{pa}$ |
| **BEHLING [111]** | Stable heart failure with moderate PH, n=22 | Sildenafil 50 mg three times daily for 4 weeks | Peak $V'_{O_2}$ and systolic $P_{pa}$ assessed by echocardiography | Sildenafil improved function capacity and $V'_{O_2}$ kinetics, and significantly reduced systolic $P_{pa}$ |
| **GUAZZI [112]** | HFPEF and systolic $P_{pa}$ >40 mmHg, n=44 | Sildenafil 50 mg three times daily for 1 year | Pulmonary haemodynamics and RV performance | Sildenafil improved pulmonary haemodynamics, RV function and dimension, LV relaxation and distensibility, and lung interstitial water metabolism |

NYHA: New York Heart Association; FC: functional class; *i.v.*: intravenous; 6MWD: 6-minute walking distance; PVR: pulmonary vascular resistance; $P_{pcw}$: pulmonary capillary wedge pressure; $P_{pa}$: pulmonary artery pressure; $P_{ra}$: right atrial pressure; SVR: systemic vascular resistance; LVESV: left ventricular end-systolic volume; MRI: magnetic resonance imaging; $V'_{O_2}$: oxygen uptake; RV: right ventricular; LV: left ventricular; PH: pulmonary hypertension; HFPEF: heart failure with preserved ejection fraction.

patients with PH secondary to heart failure and reduced LVEF improved exercise capacity, gas exchange and pulmonary haemodynamics in a dose-dependent manner [132–134]. The haemodynamic benefits were specific to the pulmonary circulation and most dramatic in patients with severe PH. The effects observed in the acute setting may also persist during longer-term treatment [108, 109]. LEWIS *et al.* [109] studied 34 patients with symptomatic heart failure, reduced LVEF and associated PH before and after randomisation to either sildenafil or placebo for 12 weeks. Sildenafil improved peak $V'_{O_2}$, PVR and cardiac output with exercise, and there was also improvement in exercise capacity and quality of life. The dose of sildenafil was 50 mg three times a day at completion of the study, which is higher than the FDA-approved dose for PAH (20 mg three times a day). It can be speculated that higher doses may offer additional benefits, particularly over longer durations of treatment. A recent study reported on six patients excluded from heart

transplantation due to severe PH; after 1 month of sildenafil (50 mg *b.i.d.*), five patients had significant reductions in PVR and TPG [135]. However, since no patient had undergone transplantation at the time of publication, the significance of the haemodynamic improvement is still unclear. Although the results observed in small, single-centre experience are encouraging, they should be treated with extreme caution, as similar results were also observed after epoprostenol and ERAs, and were contradicted by large clinical trials.

Sildenafil was investigated in 26 patients with advanced heart failure, candidates for heart transplantation in whom PH persisted after adequate LV unloading *via* recent LV assist device therapy [110]. The addition of sildenafil (50 mg three times a day for 3 months) together with continued LV assist device support substantially and rapidly lowered mean $P_{pa}$ and PVR to levels <3 Wood units without elevating $P_{pcw}$, and RV function also improved [133]. BEHLING *et al.* [111] found that sildenafil (50 mg three times a day for 4 weeks) in patients with advanced systolic heart failure substantially improved exercise capacity, ventilatory efficiency and $V'_{O_2}$ kinetics, with concomitant sustained reductions in $P_{pa}$.

Long-term use of PDE-5 inhibitors (PDE-5 I) in patients with heart failure and reduced LVEF has not been investigated to date, and there are concerns that long-term PDE-5 inhibition might produce adverse events, such as the increase in mortality seen with the PDE-3 inhibitor milrinone [136].

GUAZZI *et al.* [112] assessed the effectiveness of sildenafil in a 1-year, placebo-controlled, randomised study of 44 patients with HFPEF-PH. Sildenafil (50 mg *t.i.d.*) improved pulmonary haemodynamics, RV function and dimension, LV relaxation and distensibility, and lung interstitial water metabolism. The evolving data on the possible advantages of PDE-5 inhibition prompted the initiation of the RELAX (Phosphodiesterase-5 Inhibition to Improve Quality of Life and Exercise Capacity in Diastolic Heart Failure) trial, which is examining the effectiveness of sildenafil in patients with a clinical diagnosis of HFPEF, focusing on exercise capacity as the primary end-point.

In patients with PH secondary to valvular dysfunction, surgical correction of the failing valve is usually indicated. Several clinical studies have shown that removing the mitral valve gradient, either surgically or with percutaneous balloon valvuloplasty, will result in an immediate fall in the $P_{pa}$ [29–31]. The degree of the fall, however, can vary considerably, with some patients achieving normal haemodynamics immediately following an intervention and others taking many months to improve. FAWZY *et al.* [31] reported that in patients with mitral stenosis and severe PH, the pulmonary pressure regressed to normal levels over 6–12 months after successful mitral balloon valvuloplasty. The magnitude and rate of regression may be related to the severity of the vascular disease, which in turn may be related to the duration of PH and to constitutional factors. These may either induce more severe vascular disease or slow the reverse remodelling of the obstructive changes in the distal pulmonary arteries.

ROSENHEK *et al.* [137] evaluated the outcome of a watchful waiting strategy in patients with asymptomatic severe mitral stenosis until they were referred for surgery when symptoms occurred or when asymptomatic patients developed LV enlargement, LV dysfunction, PH or recurrent atrial fibrillation. Only five out of 132 patients followed for a median of 62 months developed new onset of atrial fibrillation or PH. These findings are in agreement with the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with valvular heart disease [61], which recommend mitral valve surgery for asymptomatic patients with chronic severe mitral stenosis, preserved LV function and PH (s$P_{pa}$ >50 mmHg at rest or >60 mmHg with exercise).

PH frequently complicates the perioperative management of patients undergoing mitral valve surgery and may be aggravated by endothelial dysfunction due to cardiopulmonary bypass procedure [138, 139]. Exacerbation of PH may result in acute RV failure, which is associated with high morbidity and mortality [140]. A recent study randomised 20 patients with chronic PH undergoing mitral valve repair to receive inhaled iloprost or *i.v.* nitroglycerine [141]. Iloprost, which was administered during weaning from cardiopulmonary bypass, selectively decreased PVR index and TPG with an associated improvement in indices of RV function, and was apparently more pulmonary selective than *i.v.* nitroglycerine. However, the real clinical benefit of these effects is not clear.

MALOUF *et al.* [142] analysed the clinical characteristics and outcomes of 47 patients (mean age 78 years) with severe PH and severe aortic stenosis. Aortic valve replacement (AVR) was performed in 37 (79%) patients and 10 (21%) patients were treated conservatively. 15 (32%) of the group that underwent AVR died, compared with 80% of the conservatively treated group. In contrast with the severity of LV systolic dysfunction or concomitant coronary artery bypass grafting, severe PH was an independent predictor of perioperative mortality. However, it seems that the prognosis for patients with aortic stenosis and severe PH treated conservatively without AVR is dismal. Although AVR is associated with higher than usual mortality, the potential benefits outweigh the risk of surgery [64]. An interesting recent study reported that a single dose of a PDE-5 I is safe in patients with severe symptomatic aortic stenosis and is associated with acute improvements in pulmonary and systemic haemodynamics, resulting in biventricular unloading [143]. However, longer-term studies to evaluate the role of PDE-5 inhibition as an adjunctive medical therapy in patients with aortic stenosis are needed.

AVR in patients with severe aortic regurgitation and PH resulted in decreased PVR and normalisation of $P_{pa}$ in most patients, with no increased mortality compared with patients with no PH [64].

## Future directions

PH is common in patients with LHD, and an increasing number of patients with severely increased $P_{pa}$ are referred to PH centres for evaluation, even when PH is moderate. In addition, PH complicating HFPEF is often misdiagnosed as PAH, resulting in inadequate use of PAH-specific therapies. The term "out-of-proportion PH" adds to the confusion, since some physicians believe it is similar to PAH. It is therefore critical to better identify the phenotype of the subgroup of patients presenting an exaggerated increase in mean $P_{pa}$ in response to the initial insult of a passive increase in left heart filling pressures. That identification is complicated by the lack of knowledge about the natural history of passive PH and the factors that contribute to the development of severe and out-of-proportion PH. It is possible that genetic predisposition and changes in cell phenotype play a role in the course of PH owing to LHD. There is also a need to better define the haemodynamic classification of post-capillary PH. Because most patients with PH-LHD essentially have an increase in s$P_{pa}$ with high pulse pressure, it might be more accurate to rely on the diastolic $P_{pa}$–$P_{pcw}$ difference rather than the TPG. The potential for reversibility and the role of vasoreactivity tests in this population need to be addressed. Because the current literature lacks consistency, there is no clear recommendation as to what should be considered reversible, or which agent should be used in the setting of PH-LHD. It has also been shown that simply unloading the left heart by implanting a LV assist device may normalise pulmonary haemodynamics.

Therapy for PH-LHD remains an unmet medical need. Randomised controlled trials have been conducted on heart failure with reduced ejection fraction using PAH-specific therapies: all of them failed to demonstrate a clinical benefit and, in some cases, even led to clinical deterioration. No large trial has been performed on the limited population of patients presenting heart failure and PH. Small trials using the PDE-5 I sildenafil in this setting have been encouraging, both in patients with preserved EF [122] and those with decreased ejection fraction [71, 72]. However, such initial positive experience needs to be confirmed in large-scale clinical trials. A phase II trial is underway with the guanylate cyclase stimulator riociguat in PH-LHD with reduced ejection fraction. Until more data are available, the use of specific PAH therapy in patients presenting PH in the context of LHD is not recommended [2].

## Conclusion

LHD is the most common cause of PH and, in most cases, complicates heart failure with or without impaired LVEF. When present, PH owing to LHD is associated with increased symptoms, impaired quality of life and poor outcome. In a sizeable subgroup of patients, the increase in mean $P_{pa}$ by factors other than the passive elevation of left-sided filling pressures leads to pulmonary vascular remodelling and significant PH. More data are needed to establish the risk factors for

developing PH in LHDs, and to better characterise this population. A first important step would be to reconsider the current definition of post-capillary PH in its ''reactive'' component. Such efforts are urgently needed as they are the first step to exploring potential therapies. In this setting, only appropriately sized and long-term randomised controlled studies can define the safety and efficacy of approved PAH drugs.

### *Statement of Interest*

None declared.


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# Chapter 11

# Pulmonary hypertension in patients with COPD

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**SUMMARY: Mild-to-moderate pulmonary hypertension (PH) is a common complication of advanced chronic obstructive pulmonary disease (COPD). The presence of PH is associated with an increased risk of acute exacerbation and decreased survival.**

**Patients with COPD may present with severe elevation of pulmonary artery pressure (mean pulmonary artery pressure >35–40 mmHg). This is observed in end-stage disease, left heart disease or another COPD-associated respiratory disorder. A small proportion of patients may develop severe PH without any concomitant heart or lung disease other than COPD. These patients have unusual cardiopulmonary abnormalities with moderate airflow limitation, severe hypoxaemia, hypocapnia, a very low diffusing capacity of the lung for carbon monoxide and pulmonary haemodynamic characteristics similar to those of idiopathic pulmonary arterial hypertension (IPAH). Survival in this latter population of COPD is severely compromised. Right heart catheterisation (RHC) is mandatory when severe PH is suspected.**

**Management of PH in COPD relies on ruling out comorbidities, optimising therapy for COPD and long-term oxygen therapy. Specific treatment developed for IPAH should not be prescribed in COPD patients outside controlled trials or experienced PAH centre.**

**KEYWORDS: Chronic obstructive pulmonary disease, nitric oxide, pulmonary heart disease, pulmonary hypertension, respiratory insufficiency**

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Chronic obstructive pulmonary disease (COPD) is defined by persistent airflow limitation that is usually progressive [1]. This chronic lung disease is also characterised by frequent associated comorbid conditions and episodes of acute exacerbation. The important lesions in the lungs of patients with COPD are the alteration of distal airways, the development of emphysema and the occurence of pulmonary vascular remodelling [2]. Once overlooked in patients with COPD, pulmonary vascular lesions and pulmonary hypertension (PH) are now recognised as central elements of disease pathogenesis [3] and are felt to be important in the development of the frequent comorbidities [4, 5].

The 4th World Symposium on PH defined group 3 as "pulmonary hypertension due to lung diseases and/or hypoxaemia" [6]. This group includes COPD. Due to the high prevalence of COPD, PH secondary to COPD is one of the most frequent causes of PH [7]. Besides the interesting links between the pathogenesis of COPD and PH, PH should be considered in COPD patients because it can impair exercise capacity and survival independently of the degree of airway obstruction [5, 7–9].

This chapter is devoted to PH due to COPD with the aim to cover definition, pathogenesis, haemodynamic characteristics, clinical impact, diagnostic strategy and management. The diagnosis and treatment of right heart failure during acute exacerbations of COPD will not be reviewed.

## Definition

The current definition of PH is a mean pulmonary artery pressure ($P_{pa}$) $\geqslant$25 mmHg. Patients from groups 1, 3 and 4 of the current classification must also have a pulmonary capillary wedge pressure ($P_{pcw}$) $\leqslant$15 mmHg and a normal or reduced cardiac output [10]. A threshold value of 25 mmHg has been generally accepted because it is clearly abnormal and almost all observational studies and randomised controlled trials dedicated to PH have selected patients according to this cut-off value. Nevertheless, it has been acknowledged, and it is particularly true in COPD, that a mean $P_{pa}$ between 21 and 24 mmHg is also abnormal [11]. Further studies in this field are needed to better understand the clinical impact of this range of mean $P_{pa}$ values (currently classified as pre-PH) [12].

A second important issue to consider in terms of definition is "out of proportion" (or disproportionate) PH. Cut-off values of mean $P_{pa}$ $\geqslant$35 mmHg [13] and $\geqslant$40 mmHg [14] have been used in the literature to distinguish out of proportion PH. This expression appears in the current European Respiratory Society/European Society of Cardiology guidelines [15] and studies have shown different haemodynamic characteristics and greater mortality in this sub-population of COPD [13, 14]. The lack of a consensus definition hinders efforts to study this entity. We propose a definition based on our clinical experience. Any PH in patients with mild or moderate ventilatory compromise (forced expiratory volume in 1 second ($FEV_1$) $\geqslant$50% of the predicted value), or a patient with a mean $P_{pa}$ $\geqslant$40 mHg, in the absence of comorbid illness, irrespective of severe ventilatory compromise. As pulmonary haemodynamics should be normal or near normal at rest in patients with a forced expiratory volume in 1 second $\geqslant$50% and because a mean $P_{pa}$ of 40 mmHg seems to be an important threshold, we suggest two criteria to define disproportionate PH in COPD.

Cor pulmonale is defined as right ventricular (RV) hypertrophy and dilatation, secondary to PH caused by lung diseases. However, cor pulmonale is not useful in clinical practice. First, the detection of RV abnormalities depends on the method employed and secondly, peripheral oedema, a clinical surrogate of cor pulmonale, might be observed in COPD patients with normal or low central venous pressure [16]. Exercise PH has been used in clinical research in COPD, although there is no consensus definition [15].

Therefore, only the definition of PH at rest (mean $P_{pa}$ $\geqslant$25 mmHg, $P_{pcw}$ $\leqslant$15 mmHg and normal or reduced cardiac output) is appropriate for routine assessment of pulmonary haemodynamics in COPD patients.

## Pathogenesis of PH in COPD

As stated previously, PH in COPD is of the pre-capillary type associated with normal or low cardiac output. Therefore, PH is mainly due to an increase in pulmonary vascular resistance (PVR). Pulmonary vascular remodelling is the main factor of increased PVR in COPD. Pulmonary vasoconstriction, pulmonary pressure swings, reduction of the pulmonary vascular

bed and blood hyperviscosity are less significant causal factors. It has been shown that cigarette smoke induces pulmonary vascular remodelling at an early stage of COPD [5]. Pulmonary endothelial dysfunction and local inflammation are linked in COPD smokers with pulmonary vascular remodelling. Chronic alveolar hypoxia induces remodelling of small pulmonary arteries and arterioles in people living at high altitude and animal models of PH. Once considered the main factor of pulmonary vascular remodelling in COPD, hypoxia has been reconsidered because pulmonary vascular changes can be observed in patients who do not have hypoxaemia and because long-term oxygen therapy does not fully reverse PH in COPD. Nevertheless, in a site of local inflammation, as observed in the vicinity of small pulmonary arteries in patients with COPD, local hypoxia might be an important associated factor of pulmonary vascular remodelling.

## Pulmonary haemodynamic characteristics

PH in patients with COPD is of the pre-capillary type; therefore, $P_{pcw}$ is normal at rest when there is no associated left ventricular (LV) comorbidity. However, an increase in $P_{pcw}$ is frequently observed in patients with severe COPD of the emphysematous type [17] and when there is an associated LV dysfunction [18].

Due to the slow rate of progression of the RV afterload, the RV has time to adapt [19]. This slow development of PH explains why RV contractility is preserved and cardiac output at rest is in the normal range in patients in a stable condition.

In COPD, as well as in other chronic respiratory diseases, PH is usually of mild-to-moderate severity [5, 7]. This characteristic makes an important distinction from group 1 and from group 4 of the current classification (table 1) [20–22].

Although, PH is mild-to-moderate at rest, $P_{pa}$ increases noticeably during sleep, exercise and acute exacerbation. Large variations of pressure due to respiratory swings are also frequently observed in COPD [22]. An illustration of a typical recording of $P_{pa}$ is shown in figure 1.

Approximately 10–20% of patients with advanced COPD have been reported to have severe PH (mean $P_{pa} \geqslant 35$ mmHg). This could be observed in three clinical situations [13, 14]. First, few patients with very severe airflow limitation, severe hypoxaemia and hypercapnia present with a significant increase in mean $P_{pa}$ at rest and in a stable state. Secondly, patients with comorbid conditions, such as chronic venous thromboembolism, severe left-sided cardiac disease or an associated restrictive lung disease, may have severe PH. Finally, severe PH has also been

**Table 1.** Comparison of pulmonary haemodynamics in three representative series of patients with pulmonary hypertension

| | Group 1 PAH | Group 3 COPD | Group 4 CTEPH |
|---|---|---|---|
| **First author [ref.]** | HUMBERT [20] | MINAI [22] | DE PERROT [21] |
| **Subjects** | 674 | 797 | 34 |
| **Age years** | 50±15 | 67±6 | |
| **FEV1 % pred** | | 27±7 | |
| **$P_{a,O_2}$ mmHg** | | 63±10 | |
| **$P_{a,CO_2}$ mmHg** | | 43±6 | |
| **Mean $P_{pa}$ mmHg** | 55±15 | 23±5 | 46±13 |
| **Cardiac index L·min$^{-1}$·m$^{-2}$** | 2.5±0.8 | 2.8±1.0 | 2.1±0.7 |

Data are presented as n or mean±SD. In chronic obstructive pulmonary disease (COPD), the mean pulmonary artery pressure ($P_{pa}$) is less increased compared with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), and cardiac output is in the normal range in most of the COPD patients. Group 1: French registry of PAH; Group 3: National Emphysema Treatment Trial; Group 4: Toronto General Hospital; FEV1: forced expiratory volume in 1 second; % pred: % predicted; $P_{a,O_2}$: arterial oxygen tension; $P_{a,CO_2}$: arterial carbon dioxide tension.

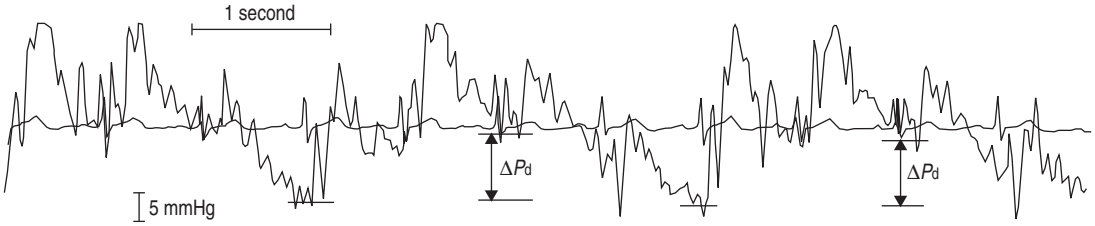


**Figure 1.** An illustration of a typical recording of pulmonary artery pressure ($P_{pa}$) showing that in patients with chronic obstructive disease, particularly those of emphysematous type, $P_{pa}$ has important respiratory swings. Mean $P_{pa}$ is 22 mmHg in this example. $\Delta P_d$: diastolic pressure change (12 mmHg in this example, normal value <4 mmHg). Reproduced from [23] with permission from the publisher.

observed in COPD patients with moderate airflow obstruction, severe hypoxaemia and hypocapnia. The latter condition has been termed out of proportion PH. Patients with this type of PH present with pulmonary haemodynamic alterations reminiscent of those seen in idiopathic pulmonary arterial hypertension (PAH). Table 2 shows $FEV_1$ values, arterial blood gases and the pulmonary haemodynamic characteristics of COPD patients with disproportionate PH [13, 14]. Recent data from the National Emphysema Treatment Trial seems to indicate that severe PH at rest is very uncommon in patients with emphysema without significant comorbidities [22].

# Clinical impact

## Dyspnoea on exertion and exercise tolerance

The main mechanisms of dyspnoea in COPD are dynamic hyperinflation, increase in ventilatory demand, respiratory muscle weakness and, in the most severe patients, hypoxaemia and hypercapnia [24]. Therefore, it is difficult to know whether PH impacts on symptoms during exercise. Few physiological studies have shown that the increase in $P_{pa}$ during exercise may contribute to dyspnoea [25, 26]. More recently, a study compared COPD patients with severe PH and mild-to-moderate airflow limitation with patients who had less severe PH but more important airflow limitation and showed that the former group of patients had more exercise intolerance [14]. It has also been shown that patients with COPD and a mean $P_{pa} \geqslant 40$ mmHg had an exhausted circulatory reserve at the end of exercise contrasting with a ventilatory limitation in COPD patients without severe PH [8]. These observations suggest that pulmonary haemodynamics play a role on exertional dyspnoea in COPD patients with severe PH (mean $P_{pa} \geqslant 40$ mmHg), but probably not in patients with moderate PH or no PH.

**Table 2.** Comparison of chronic obstructive pulmonary disease patients with pulmonary hypertension (PH) without comorbid conditions that could cause disproportionate PH compared to patients with moderate or no PH

| | Disproportionate PH | Disproportionate PH | Moderate or no PH |
|---|---|---|---|
| **First author [ref.]** | THABUT [13] | CHAOUAT [14] | CHAOUAT [14] |
| **Subjects** | 16 | 11 | 30 |
| **$FEV_1$ % pred** | 49±12 | 50 (44–56) | 29 (26–40) |
| **$P_{a,O_2}$ mmHg** | 46±16 | 46 (41–53) | 64 (56–73) |
| **$P_{a,CO_2}$ mmHg** | 40±11 | 32 (28–37) | 44 (37–47) |
| **Mean $P_{pa}$ mmHg** | 40±10 | 48 (46–50) | 21 (16–25) |

Data are presented as n, mean±SD or median (interquartile range). Remarkably, patients with disproportionate PH have less airflow limitation. $FEV_1$: forced expiratory volume in 1 second; % pred: % predicted; $P_{a,O_2}$: arterial oxygen tension; $P_{a,CO_2}$: arterial carbon dioxide tension; $P_{pa}$: pulmonary artery pressure.

### Exercise capacity

Two recent retrospective studies performed in advanced COPD patients found that high mean $P_{pa}$ was associated with a short 6-minute walking distance (6MWD) [27, 28]. In another study, patients with COPD and severe PH (mean $P_{pa} \geqslant 40$ mmHg) had lower maximal power during an incremental cardiopulmonary exercise test compared to patients with moderate or no PH while they had less airflow limitation [8]. In that latter study, end-tidal carbon dioxide tension, mixed venous oxygen saturation and the cardiac output–oxygen consumption slope were lower in COPD patients with severe PH. It has been shown that in the small population of patients with severe or disproportionate PH, 6MWD may be very low [29]. These observations showed that when mean $P_{pa}$ is $\geqslant 40$ mmHg in COPD, pulmonary haemodynamic impairment impacts exercise capacity. However, as stated before it must be emphasised that such a condition is uncommon and that a majority of COPD patients have exercise limitation due to limited ventilatory reserve.

### Survival

Before the wide-scale introduction of long-term oxygen therapy (LTOT), it was shown that PH in COPD was an independent prognostic factor [30]. Nowadays, despite the fact that LTOT improves the survival of hypoxaemic patients, PH is still associated with lower survival rates [28, 31]. Importantly, an elevated $P_{pa}$ was also associated with an increased risk of severe acute exacerbation in COPD patients with moderate-to-severe airflow limitation [32].

In conclusion, it is often difficult to differentiate the clinical consequences of PH from those of airflow limitation in COPD. Nevertheless, it is important to detect associated conditions (such as left heart disease) or severe PH, which impact on the pulmonary circulation and may have clinical consequences in order to prescribe any recommended treatment. Recent data from emphysema patients participating in the National Emphysema Treatment Trial showed that even though pulmonary haemodynamics were more abnormal among patients with a reduced 6MWD and among those who died, age and pulmonary function abnormalities remained the primary drivers of functional capacity and survival [9].

## Diagnostic strategy

Recognition of PH in COPD is difficult, especially in its mildest form because it is difficult to differentiate the clinical picture of PH from the underlying lung disease [33]. Cardiac auscultation is often hampered by thoracic distension or pulmonary sounds. Signs of right heart failure are rarely noticed in COPD except during severe acute exacerbation or in disproportionate PH. Peripheral oedema is frequent in the course of COPD, but rarely due to right heart failure. Chest radiography and ECG may be helpful but lack sensitivity. Spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide and arterial blood gases do not allow an accurate prediction of PH. Nevertheless, symptoms, clinical signs and these usual tests are useful in raising suspicion of PH. Indeed, at this stage the main pitfall is to systematically exclude PH as a cause of severe dyspnoea on exertion and/or severe hypoxaemia. It must be mentioned that when these latter characteristics are identified in patients with COPD and are not adequately explained by the severity of compromise in lung function, it is of paramount importance to search for a comorbid condition and severe PH.

A fairly good noninvasive assessment of PH can be performed with Doppler echocardiography using several measurements. The association of measurements of maximal velocity of tricuspid regurgitation, pulmonary acceleration time, and indices of RV and LV dysfunction is important to exclude LV disease and raise suspicion of PH. However, Doppler echocardiography has been shown to lack sensitivity and specificity in patients with COPD [34, 35]. Therefore, clinicians should not stop searching for PH only on the basis of a negative echocardiography when PH is suspected.

Right heart catheterisation (RHC) is the gold standard for the diagnosis of PH. It allows the direct measurement of mean $P_{pa}$, $P_{pcw}$, right heart filling pressure and cardiac output. The main disadvantage of RHC is its invasive nature.

Brain natriuretic peptide (BNP) is mainly secreted by cardiomyocytes. Severe PH leads to an increase in plasma BNP [29]. However, since PH is generally mild to moderate and left heart disease is frequently associated with COPD, it is likely that BNP would lack specificity to detect PH in the whole population of COPD patients.

As stated previously, high mean $P_{pa}$ was associated with a short 6MWD in two retrospective studies [27, 28]. In these two studies, although statistically significant, the differences of 6MWD between patients having or not having PH were low with a standard deviation corresponding to four to five times the mean difference. COPD patients with PH might have more significant exercise desaturations. Although 6MWD does not clearly allow differentiation of patients with PH, unexpected low walking distance and severe desaturations should raise suspicion of PH.

The incremental maximal cardiopulmonary exercise test displays a specific pattern in patients with COPD and disproportionate PH [8, 36]. This profile, also observed in chronic heart failure, is characterised by very low maximal work, a larger ventilatory reserve at peak exercise and a low end-tidal partial pressure of carbon dioxide compared with COPD patients with mild-to-moderate PH or no PH.

Chronic pulmonary thromboembolism, associated restrictive lung disease or sleep-disordered breathing are relatively frequent conditions known to cause PH [14]. Symptoms and signs of these comorbidities could be covered by the clinical picture of COPD. Therefore, it may also be important to perform a measurement of static lung volumes, ventilation/perfusion scans, a thoracic computed tomography angiography and a sleep study.

In conclusion, although several tests may increase the suspicion for PH, RHC is mandatory to confirm a diagnosis of PH. However, due to its invasive nature this test should not be performed in all patients with COPD. Unfortunately, there is no unique test that may be used to appropriately select patients for RHC and a comprehensive evaluation should lead one to consider performing RHC in patients with COPD (fig. 2). It must be emphasised that severe PH or diastolic (left) heart failure are difficult to diagnose without performing RHC and, if left unrecognised and untreated, could have severe consequences for the patient.

## Treatments

The objectives of PH treatment in COPD are to improve pulmonary haemodynamics, functional status and survival (table 3). Due to the complex interplay between lung mechanics, pulmonary haemodynamics and cardiac function, a single target is unlikely to be widely effective.

The underlying disease should be optimally treated. In particular, smoking cessation, among other positive effects, may help to lower the risk for PH [37, 38]. PH is not a contraindication to exercise training [39]; therefore, pulmonary rehabilitation can be performed in COPD patients with PH. However, when PH is severe it is wise to refer patients to an expert PH centre initially and monitor exercise training. When considering PH in patients with COPD it is important to consider and rule out comorbid conditions, such as left heart disease, sleep-disordered breathing, pulmonary embolism and interstitial lung disease. This is especially true of patients found to have severe or disproportionate PH and in patients with PH associated with mild-to-moderate COPD [7]. Their occurrence may help explain the PH and will have a significant impact on patient management.

Alveolar hypoxia is considered to be a cause of the elevation of PVR and $P_{pa}$ in COPD patients. One of the aims of oxygen therapy is the improvement of PH induced by chronic alveolar hypoxia. Pulmonary haemodynamic data were available at the onset in all patients and follow-up RHC was performed in a relatively high number of patients in the Nocturnal Oxygen Therapy Trial [40] and Medical Research Council studies [41]. These studies showed that $P_{pa}$: 1) increased in patients

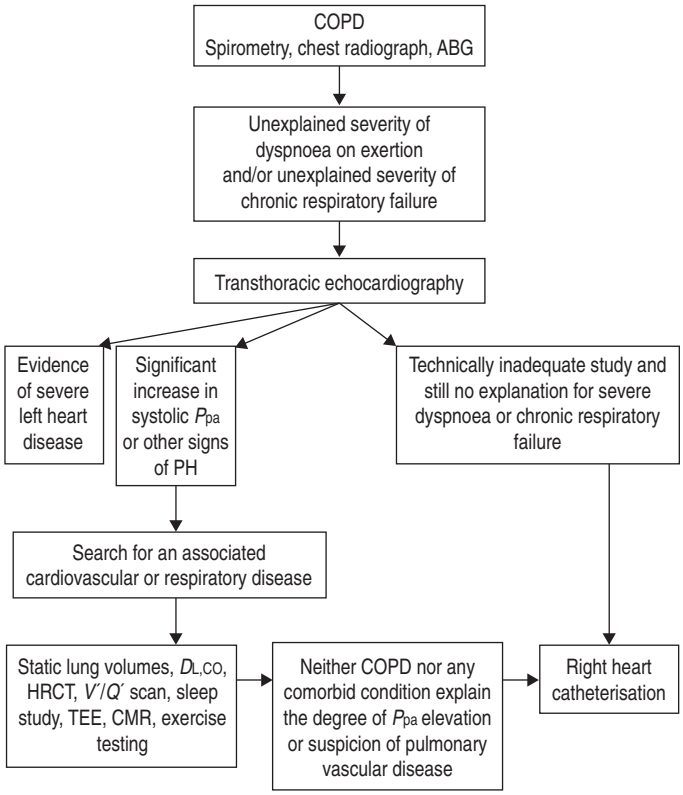
COPD
Spirometry, chest radiograph, ABG
Unexplained severity of dyspnoea on exertion and/or unexplained severity of chronic respiratory failure
Transthoracic echocardiography
Evidence of severe left heart disease
Significant increase in systolic $P_{pa}$ or other signs of PH
Technically inadequate study and still no explanation for severe dyspnoea or chronic respiratory failure
Search for an associated cardiovascular or respiratory disease
Static lung volumes, $D_{L,CO}$, HRCT, $V'/Q'$ scan, sleep study, TEE, CMR, exercise testing
Neither COPD nor any comorbid condition explain the degree of $P_{pa}$ elevation or suspicion of pulmonary vascular disease
Right heart catheterisation

**Figure 2.** Proposal of a diagnosis algorithm leading to right heart catheterisation in patients with chronic obstructive pulmonary disease (COPD). When severe left heart disease or an associated respiratory disease is highlighted, the indication of right heart catheterisation should be reconsidered after introducing an appropriate treatment. ABG: arterial blood gases; $P_{pa}$: pulmonary artery pressure; PH: pulmonary hypertension; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; $V'/Q'$: ventilation/perfusion ratio; TEE: transoesophageal echocardiography; CMR: cardiac magnetic resonance.

who were not treated with oxygen therapy; 2) remained stable in patients who received LTOT for 12–15 hours per day; and 3) slightly decreased in patients treated with continuous LTOT (>18 hours per day).

COPD patients may have significant hypoxaemia during sleep even though daytime arterial oxygen tension is >60 mmHg [42]. It has been hypothesised that isolated sleep-related hypoxaemia could lead to permanent PH. If this were the case, prescription of nocturnal oxygen therapy would be justified. In fact, the present data related to sleep desaturation in COPD are not sufficient for justifying the use of nocturnal oxygen therapy in COPD patients who do not qualify for conventional LTOT [43]. A large ongoing multicentre trial of supplemental oxygen for patients with COPD and moderate hypoxaemia in North America will probably answer to this question [44].

Patients with an associated obstructive sleep apnoea syndrome or restrictive lung disease may need oxygen therapy plus continuous or bi-level positive airway pressure support [45]. This latter treatment is often necessary to stabilise chronic hypercapnic respiratory failure and may help to improve PH.

It is important to know whether any therapy, other than LTOT, acting on the pulmonary circulation is able to improve pulmonary haemodynamics and the clinical status of patients with COPD. To date, all attempts at using pulmonary vasodilators to improve outcomes in patients with COPD have been disappointing. Vasodilators, such as calcium channel blockers and urapidil, acutely decrease RV afterload but no long-term beneficial effect has been reported [5]. Similar results have been shown with angiotensin inhibitors [46]. Thus, calcium channel blockers, angiotensin inhibitors and $\alpha_1$-antagonists should not be prescribed to treat PH in patients with COPD.

At present, the main approach to treating patients with PAH is to correct, at least partially, the pulmonary endothelium dysfunction [47]. Given that the unbalanced release of endothelium-derived mediators has also been observed in PH due to COPD, drugs acting on or correcting the pulmonary endothelial dysfunction have been tested in patients with COPD. Inhaled nitric oxide and sildenafil have an acute positive effect on pulmonary haemodynamics [48, 49]. Sildenafil decreases mean $P_{pa}$ and total PVR at rest and during exercise while worsening arterial hypoxaemia. A 3-month randomised trial of inhaled nitric oxide plus oxygen supplementation *versus* placebo plus oxygen supplementation showed a persistent improvement of mean $P_{pa}$, PVR and cardiac output [50]. These results are promising but technical and safety issues are far from

**Table 3.** Recommendations regarding the management of pulmonary hypertension (PH) due to chronic obstructive pulmonary disease (COPD)

| | Mild/moderate COPD | Severe COPD |
|---|---|---|
| **Optimise COPD management** | Yes | Yes |
| **Rule out comorbidities** | Yes | Yes |
| **Confirm diagnosis** | Right heart catheterisation | Right heart catheterisation |
| **Oxygen supplementation** | If needed<br>Look for exertional and nocturnal hypoxia | If needed<br>Look for exertional and nocturnal hypoxia |
| **Pulmonary rehabilitation** | If needed | Yes |
| **PH-specific therapy** | Consider in the context of a clinical trial<br>Potential functional and survival benefits are not known | Consider in the context of a clinical trial<br>May provide short-term functional benefit<br>Survival benefit not known |
| **Lung volume reduction surgery** | Contraindicated[#] | Contraindicated[#] |
| **Lung transplantation** | Consider if disease progressing despite above recommendations | Yes<br>Most likely to provide functional benefit |

[#]: in patients with significant PH.

being resolved. In a 3-month randomised controlled trial of COPD patients, some of whom had PH, bosentan did not improve 6MWD and was responsible for a worsening of gas exchange and deterioration in health-related quality of life [51]. Despite these limited data, patients with PH due to COPD in North America are being treated with medications that target the pulmonary vasculature [52]. No randomised controlled trial has been performed in patients with disproportionate PH in patients with COPD.

Recent pathophysiological studies have suggested an alteration of cellular lung repair in COPD, which could lead to PH [4]. As a consequence, medications such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, with a protective effect on vascular destruction and abnormal repair at the cellular level, require further study.

Lung volume reduction surgery (LVRS) is a treatment of severe emphysema. The National Emphysema Treatment Trial showed no significant increase in mean $P_{pa}$ 6 months after LVRS when the initial value was <35 mmHg [53]. Conversely, when the mean $P_{pa}$ is >35 mmHg lung transplantation may be considered in appropriately selected candidates without significant comorbidities.

In summary, optimising COPD management and ruling out comorbid conditions are essential components of evaluation. LTOT should be prescribed in all COPD patients with PH and with an arterial oxygen tension <60 mmHg. In patients with COPD and moderate PH, treatment with PH-specific therapy is not recommended in clinical practise and should be considered in the context of a clinical trial or an experienced PAH centre. Concerning patients with severe and disproportionate PH, lung transplantation may be considered in appropriately selected candidates as it provides the best opportunity for long-term benefit.

## Five unanswered practical questions

There are currently five unanswered practical questions about PH in COPD. 1) What is the prevalence of PH in the whole COPD population? 2) What level of PH has a clear impact on the clinical status? 3) What is the definition of disproportionate PH, taking into account pulmonary haemodynamic and lung function data? 4) What is the diagnostic strategy, with a high negative predictive value and an acceptable positive predictive value, to avoid unnecessary RHC? 5) In the population of COPD with PH, who might benefit from specific PAH therapy?

## Conclusion

PH is a frequent complication of COPD. Even though frequently moderate, PH has an impact on functional capacity and survival in these patients. The impact of PH on exercise capacity is more significant when the mean $P_{pa}$ is >40 mmHg. Clinicians should suspect PH when dyspnoea on exertion and severe hypoxaemia cannot be explained by the severity of alterations in lung mechanics. Patients with moderate PH and who are hypoxaemic should be treated with LTOT and all other treatments according to current guidelines for the management of COPD. A subset of COPD patients, probably <5%, develop disproportionate PH. This latter condition shares pulmonary haemodynamic similarities with PAH and mortality is significantly increased in these patients. Due to the severity of disproportionate PH in COPD and its scarcity, patients with this condition should be referred to an expert PH centre for management.

### *Statement of Interest*

O.A. Minai is a member of the Scientific Advisory Board for Actelion, Gilead, United Therapeutics, Pfizer and Bayer, and is a member of the Speakers Bureau for Actelion, Gilead, United Therapeutics and Pfizer.

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# Chapter 12

# Pulmonary hypertension in patients with idiopathic pulmonary fibrosis

*Steven D. Nathan*[*] *and Vincent Cottin*[#,¶]

**SUMMARY: There is a growing body of evidence that pulmonary hypertension (PH) is relatively common in patients with idiopathic pulmonary fibrosis (IPF). PH in IPF is associated with increased dyspnoea, decreased exercise capacity, greater oxygen requirements, lower diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) and reduced survival. Pulmonary haemodynamics do not correlate with pulmonary function testing. The pathogenesis is complex and multifactorial, and includes lung destruction, intrinsic vascular abnormalities, hypoxia, alterations in mediators, dysregulation of neovascularisation and microvascular injuries. Additionally, comorbidities, particularly concomitant emphysema, thromboembolic events, cardiac diastolic dysfunction and obstructive sleep apnoea (OSA) may increase the risk of PH in IPF. No screening recommendations are available but right heart catheterisation (RHC) is the diagnostic procedure of choice. As yet, no studies of pulmonary vasoactive agents have demonstrated clinical efficacy; however, further trials are sorely needed. If PH therapy is considered on a case-by-case basis, particular attention must be paid to the potential benefits and possible risks, particularly worsening of gas exchange.**

**KEYWORDS: Keywords: Pulmonary fibrosis, pulmonary hypertension**

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Idiopathic pulmonary fibrosis (IPF) is a fatal progressive fibrotic disease with a median survival of 2.5–3.5 years [1–3]. It is more common in males and the elderly, with a median age at diagnosis of 65–70 years [1, 2]. There are no proven universally accepted therapies for IPF aside from lung transplantation, although several promising medical therapies are currently under evaluation [4, 5]. There is a growing appreciation that IPF is a disease whose prevalence is increasing, with data both from the UK and the USA attesting to this [6, 7]. The prognosis of IPF is difficult to predict on an individual basis, with patients running a variable course, from those who present acutely and succumb quickly to those who have a protracted course and live 5 years or more [1, 2, 8]. A variety of individual predictors of survival in IPF have been reported, including clinical predictors, physiological

parameters (pulmonary function tests and exercise capacity), histopathology (fibroblastic foci) and biomarkers [2]. Indeed, there appear to be many IPF phenotypes that present and behave differently.

Pulmonary hypertension (PH) can complicate the course of almost all forms of diffuse parenchymal lung disease [9] and is mostly categorised as group 3, as per the most recent Dana Point classification [10]. In IPF, there is a growing body of evidence attesting to supervening PH as a relatively common occurrence, even in patients with "mild" disease [11, 12]. Once PH develops, it tends to be associated with poorer functional status, greater oxygen requirements and worsened outcomes [13–15]. However, it is uncertain whether the PH itself drives this or whether the elevated pressures are a surrogate for other undetected untoward sequela of the disease. In this chapter, we will focus on the potential causes and contributory factors that may be important in the development and potentiation of PH. Important comorbidities will be discussed, as will the clinical features and ancillary studies that might suggest the presence of PH. The uncertain role of therapies directed at PH of IPF will be addressed. Finally, we will attempt to identify important areas for future research.

## Prevalence and natural history of PH in IPF

There have been many studies addressing the prevalence of PH in IPF. Most of these have been in patients with more advanced disease, including those who are being evaluated as potential lung transplant candidates. Prevalence has been shown to be anywhere from 8% to 86% (fig. 1) [12–23]. This wide range may reflect the stage at which PH was sought as well as the criteria used. For example, the 86% prevalence estimate was documented in a study of patients who received right heart catheterisation (RHC) at the time of their lung transplant [18]. The lower estimate of ~10% prevalence was a surprise finding amongst patients with "early" disease enrolled in a prospective treatment trial of ambrisentan, who had a mean disease duration of less than 1 year and a mean forced vital capacity (FVC) of 70% predicted [12]. A further ~5% of enrolled patients had haemodynamic evidence of group 2 PH related to left heart disease. Overall, PH is uncommon during the first year of the disease course in patients with IPF (and without comorbidities such as emphysema), but it may be present at RHC in ~30–45% of patients evaluated for lung transplantation and may develop in a majority of the patients later in the course of the disease [18].

PH is generally more prevalent in patients with worse lung function and a longer duration of disease (table 1 and fig. 1). Age, the need for supplemental oxygen therapy and reduced exercise tolerance are also associated with PH in IPF. The haemodynamic severity of PH in the context of IPF generally appears mild, with ~50% of patients having a mean pulmonary artery pressure ($P_{pa}$) of 25–30 mmHg [13]. Nonetheless, severe PH may still be found, albeit in a minority of patients. In the largest study to date, performed in 2,525 patients listed for lung transplantation in the USA, the mean±SD $P_{pa}$ was 34.2±9.9 mmHg and the cardiac index was 2.8±0.8 $L \cdot min^{-1} \cdot m^{-2}$ in those who underwent RHC [16]. However, only ~9% had severe PH, as evidenced by a mean $P_{pa}$ of >40 mmHg [16]. In another study of 79 patients evaluated for lung

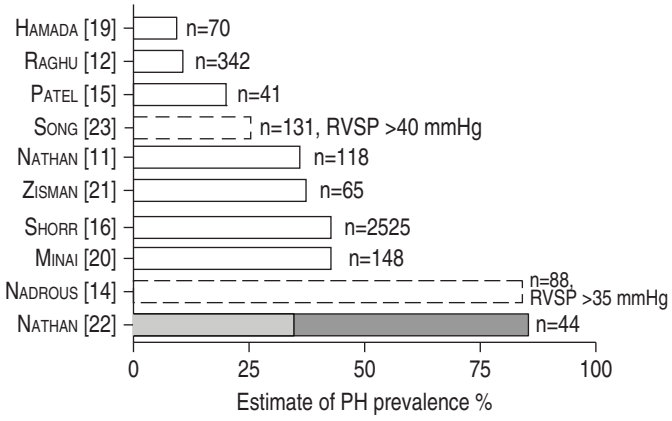


**Figure 1.** Overview of studies of pulmonary hypertension (PH) in idiopathic pulmonary fibrosis. Percentage figures indicate the estimate of PH prevalence. Solid lines indicate where diagnosis was *via* right heart catherterisation; dashed lines indicate where diagnosis was *via* echocardiography. The light grey shading alongside the study by NATHAN *et al.* [22] indicates the prevalence at time of evaluation for lung transplantation; the dark grey shading indicates the prevalence at the time of lung transplantation. RVSP: right ventricle systolic pressure.

**Table 1.** Haemodynamics and pulmonary function tests in published series of patients with pulmonary hypertension (PH)[#] and idiopathic pulmonary fibrosis

| First author [ref.] | Subjects n | FVC % | $D_{L,CO}$ % pred | $P_{a,O_2}$ mmHg | Mean $P_{pa}$ mmHg | CI $L \cdot min^{-1} \cdot m^{-2}$ | % with PH |
|---|---|---|---|---|---|---|---|
| LETTIERI [13] | 79 | 49 | 31 | NR | 30 | 3.2 | 32 |
| SHORR [16] | 2525 | 48 | NR | 41 | NR | 2.8 | 46 |
| ZISMAN [24] | 61 | 54 | 30 | 58 | 34 | NR | 39 |
| NATHAN [22] | 60 | 51 | 30 | NR | 25 | NR | 35 |

FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide % pred: % predicted; $P_{a,O_2}$: arterial oxygen tension; $P_{pa}$: pulmonary artery pressure; CI: cardiac index; NR: not recorded. [#]: defined as a mean $P_{pa}$ of $\geqslant$25 mmHg and a pulmonary capillary wedge pressure of $\leqslant$15 mmHg at right heart catheterisation.

transplantation, only ~2% had a mean $P_{pa}$ of >40 mmHg [13]. Furthermore, the haemodynamic profile of PH related to IPF is generally less severe than the PH associated with pulmonary Langerhans' cell histiocytosis (PLCH) [25, 26] or sarcoidosis. However, it tends to be more severe than PH associated with other forms of interstitial lung disease, such as lymphangioleiomyomatosis [27], or to PH related to chronic obstructive pulmonary disease (COPD) [28].

The natural history of PH in the setting of IPF has not been well documented. One study evaluating PH by serial RHC (at the time of evaluation for lung transplantation and at the time of actual transplant) did show that the PH tends to be progressive in this setting [18]. Indeed, in some of these patients, the follow-up RHC did attest to a $P_{pa}$ with almost systemic elevations. However, it not known whether the PH is progressive because of vasculocentric events or whether the increases in pressure are a surrogate for progression of the parenchymal disease and chronic respiratory failure.

## Clinical impact and prognosis

PH in IPF is associated with decreased exercise capacity, as measured by the 6-minute walk test (6MWT). PH is typically accompanied by both a decreased distance and worse desaturation during the course of the test [13, 14, 19, 29, 30]. PH diagnosed *via* gold-standard RHC or echocardiographic estimates of the right ventricle systolic pressure (RVSP) have universally demonstrated that the presence or suggestion of PH is associated with greater mortality. In one study of RHC-documented PH, patients with PH had a 1-year mortality of 28% *versus* only 5.5% in those without PH [13]. In addition, there does appear to be a dose-dependent effect, with higher pressures associated with worse outcomes. In two echocardiography-based studies performed in IPF patients with a RVSP of $\geqslant$50 or 60 mmHg, the 1-year mortality was in excess of 50% [14, 23]. In one series of patients with the syndrome of combined pulmonary fibrosis and emphysema (CPFE), the 5-year survival was only 25% in patients with a RVSP of $\geqslant$45 mmHg as compared with 75% in those with a RVSP of <45 mmHg [31]. In one study of patients with PH associated with diffuse parenchymal lung disease (including but not restricted to IPF), an elevated pulmonary vascular resistance (PVR) was strongly associated with early mortality after adjustment for age, sex, composite physiological index and IPF diagnosis [32]. Interestingly, in that study, the mean $P_{pa}$ did not discern survival. This raises the issue of which haemodynamic parameter is most important prognostically in the context of IPF. One of the areas of further research might be to explore whether it is the systolic pressure, the mean pressure (and level thereof) or the cardiac index that best discerns survival.

PH is one of numerous individual predictors of survival identified in IPF [2]. As RHC is invasive and echocardiographic estimates of RVSP have inherent limitations, the use of PH as a routine predictor of prognosis in patients with IPF may not be practical in most settings. Therefore, clinical prediction models may provide a more practical tool for individual patient management. In addition, there are very few studies that account for the prognostic significance of a large

number of variables, and it is generally not known whether PH independently predicts mortality when a broader array of parameters are included into such hypothetical models. Of all the pulmonary function parameters, it appears that the diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) might be the best for reflecting pulmonary vascular involvement. Indeed, in a large study of patients with IPF [33], the $D_{L,CO}$ % pred and 24-week change in $D_{L,CO}$ were independently associated with a worse outcome, but data regarding PH were not available.

## Pathogenesis

The pathogenesis of PH in IPF is likely to be complex and multifactorial (fig. 2), involving destruction of the lung tissue by the fibrotic process, intrinsic vascular abnormalities, hypoxia, alterations in the cytokine milieu, dysregulation of neovascularisation and endothelium-derived vasoactive mediators, comorbid conditions, and microvascular injury. The vasculopathy in IPF consists of intimal and medial remodelling of the pulmonary arteries, suggesting intrinsic mechanisms of PH independent of the fibrotic process. Although the progressive fibrosis and concomitant loss of pulmonary vasculature certainly play a role, there is a lack of correlation between PH and measures of fibrosis. The loss of pulmonary vasculature is especially likely to play a role in patients with CPFE. However, even in the absence of emphysema, the extent of fibrosis on computed tomography (CT) evaluation and the degree of restrictive physiology on pulmonary function testing have been shown to correlate poorly with underlying PH. Indeed, patients with well-preserved lung volumes appear equally predisposed to the development of PH [18]. As a pathological correlate to this, there may be vasculopathic changes in areas of the lung that are relatively unaffected by the disease process. Why some patients with mild fibrosis develop PH and others with severe fibrosis do not is uncertain. In addition to other factors being involved in the genesis of PH, this observation does raise the issue of whether there are some patients who are genetically predisposed and whether IPF with PH represents a distinct IPF clinical phenotype.

It is well recognised that hypoxia can induce vasculopathic changes. IPF patients are predisposed to hypoxia through the fibrotic process and associated ventilation/perfusion mismatching. It is also possible that unrecognised episodes of intermittent hypoxia, either nocturnal or exercise-induced, may play a role. In addition, due to the heterogeneous nature of the disease, there might be areas of the lung that are more prone to local or regional hypoxia without evidence of systemic desaturation. However, vascular remodelling and PH in IPF are not reversible with oxygen, and PH can occur in patients with mild IPF and moderate hypoxaemia [12], suggesting that hypoxia is not the only cause of PH in this setting. Fibrosis with a perivascular distribution may affect the capacitance of the vessels and their ability to accommodate blood flow without a rise in pressure. This is exemplified by a distinct flow/pressure profile at exercise, with a greater rise of pulmonary pressure and a lesser increase of cardiac output at exercise in patients with IPF as compared to non-IPF interstitial lung disease patients [34]. The fibrotic process may also result in vasculature distortion and shear

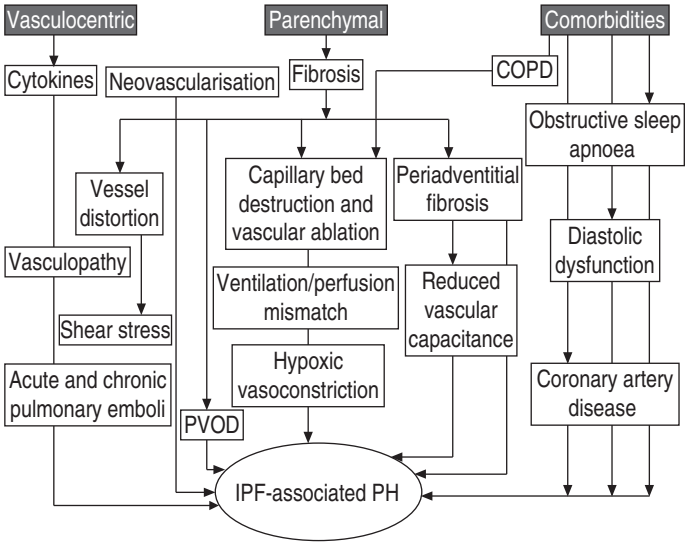


**Figure 2.** Schematic representation of the pathophysiology of pulmonary hypertension (PH) in idiopathic pulmonary fibrosis (IPF). COPD: chronic obstructive pulmonary disease; PVOD: pulmonary veno-occlusive disease.

stress, which could perpetuate the vasculopathic changes. Aberrant neovascularisation in IPF may also contribute to increased vascular resistance.

The cytokine milieu associated with the complex pathogenic process that characterises IPF may have vascular remodelling consequences, with areas of both angiostasis and angiogenesis. The physiological consequence of these cytokine-induced changes may be an elevation of the $P_{pa}$ [35]. The cytokines that may play a role in this regard include endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), pigment epithelium-derived factor (PDGF), transforming growth factor (TGF)-β, platelet-derived growth factor, endostatin, angiostatin, fibroblast growth factor-2 and angiotensin-II [35]. It also appears that those patients with PH in the context of IPF have a distinct genomic fingerprint, implying pathophysiological mechanisms that are distinct from idiopathic pulmonary arterial hypertension (IPAH) [36–38].

There also appears to be injury at the microvascular level that plays a role in the pathogenesis of IPF. Elevated factor VIII levels indicative of endothelial cell injury have been reported in IPF. It has been hypothesised that this early injury may set the stage for the subsequent development of parenchymal fibrosis [39]. Patients with IPF have a pro-thrombotic propensity, and formation of microthrombi may contribute to the genesis of PH. Therefore, it is conceivable that at the beginning stages of the pathogenic process a subgroup of patients are predisposed to develop PH through these early vasculopathic events [39, 40]. This could help to explain PH in the context of patients with mild fibrosis [12].

Histopathological examination of IPF lungs has demonstrated the presence of pulmonary veno-occlusive-type lesions in up to two thirds of IPF patients. This might be a consequence of the heterogeneous distribution of the disease process with localisation of fibrosis in a perivenular distribution. Whether the veins and venules are "innocent bystanders" to the fibrotic process or whether there is more of a primary "venopathy" is immaterial to the potential role that these lesions could play in the pathogenesis of PH [41].



## The role of comorbidities

IPF tends to be a disease of the elderly and, therefore, there is a propensity for a spectrum of comorbidities. However, even after age adjustment, IPF patients do appear to be unusually predisposed to a number of comorbidities, which may be important in the genesis or perpetuation of PH.

### Obstructive sleep apnoea

Moderate to severe obstructive sleep apnoea (OSA) characterised by apnoea/hypopnoea indices of >15 events per hour, has been described in approximately two-thirds of IPF patients [42]. Most of the events tend to be hypopnoeas, which does not diminish the theoretical impact of the associated desaturations on the development of PH. The propensity to desaturate at night is greater in these patients due to the influence of their parenchymal lung disease and the accompanying lower tidal volumes while sleeping [42]. Their reduced lung compliance, resulting in increased work of breathing and greater negative intrathoracic pressure, could conceivably predispose to upper airway collapse. However, whether sleep apnoea affects the risk of developing PH, or indeed IPF itself, remains unknown; this is an area that warrants further study.

### CPFE syndrome

A distinct IPF phenotype appears to be the CPFE syndrome (fig. 3), which has been described in 28–33% of patients [43–46]. With the high prevalence of current or prior cigarette smoking amongst IPF patients, it is not surprising that the most common of the obstructive and interstitial diseases might on occasion co-exist. Indeed, of the reported CPFE cases in the literature, 98% of them were current or former smokers [47]. However, despite this very strong association, it remains uncertain what component of emphysema is related to smoking or possibly to the traction

effect of fibrosis. Conversely, emphysema associated with interstitial lung disease may alter the high-resolution CT (HRCT) appearance, such that co-existence of emphysema and a pathologically proven pattern of nonspecific interstitial pneumonia may give rise to an imaging pattern that mimicks honeycombing [48, 49]. Since the two coexisting disease processes have counterbalancing influences on lung volumes, these patients can have relatively normal lung volumes in the context of significant parenchymal lung disease [31]. A frequent clue to the presence of CPFE is a disproportionately reduced $D_{L,CO}$. Patients with PH in CPFE [50] tend to have greater reductions in the $D_{L,CO}$ and higher elevations in $P_{pa}$ than those with PH in the context of IPF [13, 16]. It is likely that this reflects the synergistic effects of pulmonary vascular impairment by both disease processes. Indeed, complicating PH is a common occurrence in CPFE with a reported prevalence of ~50% [31]. An issue of controversy is whether patients with CPFE have a better or worse prognosis than patients with isolated IPF [51]; however, it is clear that those with complicating PH do have poorer outcomes [31, 47, 50].

**Figure 3.** High-resolution computed tomography of the chest in a patient with combined pulmonary fibrosis and emphysema and pulmonary hypertension. Note the heavy coronary calcification (arrow), indicating the presence of severe underlying coronary artery disease.

## Thromboembolism

Patients with IPF have a greater propensity for thromboembolic events, which could play a role in the perpetuation of PH. There appears to be a link between venous thromboembolism (VTE) and IPF, with an increased incidence of deep venous thrombosis preceding the diagnosis having been demonstrated [52, 53]. It has also been postulated that subclinical small pulmonary emboli may lead to progressive pulmonary fibrosis [53]. Indeed, pulmonary embolism is reportedly the cause of death in 3% of cases and is associated with younger age of death in IPF patients [54, 55]. However, overt chronic thromboembolic PH (CTEPH) is quite rare in patients with IPF. This may, however, be a difficult diagnosis to attain, as the parenchymal changes of IPF can result in a false-positive high-probability ventilation/perfusion scan. It is possible patients are predisposed to thromboembolism by extraneous factors such as inactivity, steroid therapy, concomitant bronchogenic carcinoma or other associated comorbidities, but taken together these factors are unlikely to explain all thromboembolic events. There is an emerging awareness of a thrombophilic, hypercoagulable state with a high prevalence of antiphospholipid antibodies reported in IPF [39, 55]. Additionally, there is a growing appreciation of the possible role or procoagulant and antifibrinolytic pathways in the fibrotic process [39, 52]. It is therefore conceivable that local imbalances in coagulation factors could contribute to microscopic *in situ* thromboses [35].

## Cardiac diastolic dysfunction

Heart failure, specifically diastolic dysfunction, is a frequently accompanying comorbidity, which is unsurprising given that IPF is a disease of the elderly. Approximately 16% of IPF patients undergoing RHC have been demonstrated to have elevated pulmonary capillary wedge pressures ($P_{pcw}$) [11]. These were generally younger patients who mostly underwent catheterisation in the context of work-up for lung transplantation; this might therefore be an underestimation. Indeed, echocardiographic evidence of impaired left ventricular (LV) diastolic filling appeared to be fairly ubiquitous in a group of 22 IPF patients with echocardiography-based mild to moderate PH [56]. The high prevalence of diastolic dysfunction could partly be explained by the apparent greater propensity for ischaemic heart disease in patients with IPF [52, 57–59].

# Detection and diagnosis of PH in IPF patients

## Clinical signs and pulmonary function

Since the PH of IPF tends to be mild in most patients, it can be difficult to diagnose based on clinical findings. Although a loud $P_2$ heart sound, systolic tricuspid regurgitation murmur, hepatomegaly, venous jugular pulse or mild lower limb oedema might occasionally be noted, the typical findings of right heart failure are notoriously absent. However, there are important clinical clues that should alert the clinician to the possible presence of supervening PH. Despite the poor correlation between the degree of restriction measured with pulmonary function tests, there is an association in a given individual between PH and the $D_{L,CO}$. For example, patients with a $D_{L,CO}$ <40% pred are ~10 times more likely to have PH [13]. In a similar manner to pulmonary arterial hypertension (PAH), the 6MWT is emerging as an important ancillary tool in IPF. This test imparts functional data and independent prognostic information, which is likely to be due to the impact of supervening PH. The suspicion for occult PH should be heightened in the context of a 6MWT that is limited in distance and by excess desaturation, especially if these do not appear to be fully explained by the degree of restrictive disease. An important adjunct that can be gleaned from the 6MWT is the pulse rate recovery. This can be easily obtained at the end of the study and is calculated by subtracting the heart rate after 1 minute of recovery from the heart rate at the end of the 6MWT. A pulse rate recovery of <13 beats per minute has been shown to be a powerful predictor of outcomes in IPF and to be predictive of underlying PH [60].

A formula that can be used to evaluate the probability of PH in patients with IPF has been derived from the ratio of FVC % pred to $D_{L,CO}$ % pred and room air resting pulse oximetry. It was shown that a cut-off of 25 mmHg for the formula-estimated mean $P_{pa}$ had a sensitivity, specificity, positive predictive value and negative predictive value for RHC-confirmed precapillary PH of 71, 81, 71 and 81%, respectively [24]. A lower mean $P_{pa}$ cut-off of 21 mmHg increased the performance characteristics of the formula with a sensitivity, specificity, positive predictive value and negative predictive value of 95, 58, 51 and 96%, respectively [24]. However, this formula is unlikely to gain momentum in the clinical setting as it is a little tedious to calculate and the significance of a mean $P_{pa}$ of >21 mmHg remains to be determined. It also remains to be determined whether it is practical to use this or similar formulas incorporating other predictive parameters in clinical practice. Nonetheless, this does raise the concept of using multiple criteria in a Bayesian approach to increase the accuracy of predicting the presence of underlying PH.

## Thoracic imaging

The presence of an enlarged pulmonary artery segment on chest radiography has previously been shown to correlate with mortality; however, a more recent study failed to demonstrate a relationship between pulmonary artery size on CT and the presence of PH [21]. A composite of the size of the main pulmonary artery in relation to the ascending aorta, together with echocardiography-derived RVSP improves the performance characteristics of both in predicting the presence of PH [61].

## Biomarkers

Biomarkers are sorely lacking as indicators of disease presence or prognosis in IPF. However, the brain natriuretic peptide (BNP) has been shown to be both associated with the presence of PH and to be a predictor of mortality in IPF [62]. Despite this association, the BNP level has not been validated as a screening tool for PH in IPF patients. Endothelin levels are another potential biomarker; they have been shown to correlate with both PH and outcomes in IPF. Genomic analysis has also revealed a distinctive fingerprint for those patients with IPF complicated by PH [36]. However, the latter two tests are not commercially available and are therefore impractical to implement on a routine basis.

### Echocardiography

Although echocardiography has been the modality by which the importance of PH in IPF has been demonstrated in a number of studies, its role remains that of a screening tool, with RHC firmly entrenched as the diagnostic gold standard. It has been demonstrated that echocardiography may not only overestimate the true systolic $P_{pa}$ but can also underestimate or even miss the presence of PH in IPF [22, 63]. In this regard, estimation of the RVSP *via* echocardiography might only be possible in slightly more than half of IPF patients [22, 63]. Therefore, the lack of a reported elevated RVSP on echocardiography does not rule out the presence of PH, and in many cases, this may not suffice as a stand-alone test to screen for PH.

### Right heart catheterisation

As with all forms of PH, the definitive diagnosis in IPF is based on RHC. Aside from obtaining accurate measurements of pulmonary pressure, cardiac output and PVR, it is essential for the differentiation of pre-capillary PH from pulmonary venous hypertension secondary to LV systolic or diastolic dysfunction. It has also been shown that PVR is especially important in patients with IPF [32], while the cardiac index is key in providing a prognosis in patients with the CPFE syndrome and complicating PH [50]. Unlike PAH, vasoreactivity testing has no role in the management of PH associated with IPF, unless it is in the context of a research protocol.

As there are limited definitive data supporting the use of PH-specific therapy in the setting of IPF, there is a general unwillingness to subject patients, especially the more elderly, to this somewhat invasive diagnostic procedure. As a result, recommendations about when and in whom to perform RHCs are lacking. In the absence of consensus guidelines, we suggest that RHC should be performed in IPF in the following circumstances: 1) in patients being evaluated for lung transplantation; 2) where clinical worsening is disproportionate to ventilatory impairment (especially in the context of $D_{L,CO}$ <40% pred and/or combined emphysema); 3) when an accurate prognostic assessment is deemed to be critical; 4) when severe PH is suspected and off-label treatment options are being considered; and 5) where there is suspicion of diastolic dysfunction and categorisation of the wedge pressure might alter management.

## Treatment

As PH in IPF is associated with a worse outcome and reduced functional status, it would appear to make intuitive sense that this would represent a target for therapy. The primary disease that might be fuelling the process should be addressed first. However, as there are no proven universally accepted therapies that reverse IPF, this is not as yet a viable treatment approach. Although pirfenidone is now approved for the treatment of IPF in Europe and Japan, there is no evidence that this impacts on any pre-existing PH or delays the development of PH in those who are so predisposed. PH complicating IPF should prompt an evaluation for lung transplantation in patients without any contraindication; however, the majority of patients in this setting are older than the age limit for lung transplantation and present with significant comorbidities.

As with all forms of PH, any underlying contributory factors should be sought and treated when present. In the case of IPF, there should be a high index of suspicion for diastolic heart failure, venous thromboembolic disease and particularly OSA, as these could contribute to the presence and severity of PH. Supplemental oxygen therapy should be initiated whenever appropriate, although its clinical benefit has not been evaluated in IPF. There is no recommendation regarding the use of diuretics; however, they are often used in patients with peripheral oedema or where there is other evidence of right-sided heart failure. There does not appear to be a role for anticoagulation in IPF, based on the negative outcome from the US National Institutes of Health (NIH)-sponsored ACE-IPF (AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis) study, which evaluated coumadin therapy in patients with advanced IPF [64]. This study was halted early by the data safety

monitoring board for increased complications and mortality in the treatment arm. Although PH was not specifically sought in this study, it is likely that many of the patients did have this by virtue of their advanced disease. There is also no role for calcium channel blockers (CCBs) in patients with PH associated with IPF.

The availability of seven approved compounds for the treatment of PAH in both Europe and the USA raises the question of whether the PH of IPF might be responsive to targeted vasodilator therapy. When considering such therapies, it is important to be aware of the potential downsides that exist and the risk of doing more harm than good. Any vasoconstriction in the context of parenchymal lung disease is adaptive to the local milieu; amelioration of this might result in increased perfusion to relatively poorly ventilated areas, thereby compromising the oxygenation [65]. This raises the issue of the goal of such therapy; since even in the context of increased ventilation/perfusion mismatching, if relief of the PH results in an improved cardiac output, then this might be sufficient to overcome worsening oxygenation and ultimately result in improved tissue oxygen delivery. Another potential pathologic confounder is that the fibrotic process can result in pulmonary veno-occlusive-type lesions in up to two-thirds of cases [41]. Due to the heterogeneous nature of IPF disease distribution, these lesions might not be ubiquitous, and reports of pulmonary oedema induced by PAH therapy in IPF are scarce. Additionally, the dual receptor ET-1 antagonist bosentan and phosphodiesterase type-5 inhibitors (PDE-5 I) generally seem to be well tolerated in IPF patients [65–71]. Nonetheless, the potential does still theoretically exist that pulmonary oedema might be precipitated in some cases.

Despite these cautionary caveats for pulmonary "vasodilator" therapy, a number of case series attest to the potential benefit of PH-targeted therapies in patients with IPF. To date, there have been four prospective, double-blind, randomised, placebo-controlled studies of PH therapies in the context of IPF (table 2). The first of these was the Active study of inhaled iloprost in 51 patients [72]. This was essentially a negative study based on the primary end-point of 6MWT distance, with a trend towards the placebo arm doing better than the treatment group. However, this study had significant limitations; for example, PH was diagnosed based on echocardiography rather than RHC.

The second was a pilot study using sildenafil, which did not significantly increase 6MWT distance or decrease the Borg dyspnoea index [71]. The third was the NIH IPF Network study of sildenafil [70]. Although patients were not included based on RHC data, the trial involved patients with associated PH, as the inclusion criteria demanded a $D_{L,CO}$ of <35% pred for enrolment. This study of 180 patients was also negative, based on the primary end-point of a 20% change in the 6MWT distance.

**Table 2.** Clinical trials in pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF)

| Study | Lung disease type | Subjects n | Study type | Therapy | Outcome |
|---|---|---|---|---|---|
| GHOFRANI [65] | Lung fibrosis | 16 | Open-label RCT | Sildenafil, iNO, epoprostenol | Sildenafil inproved pulmonary haemodynamics and gas exchange |
| COLLARD [66] | IPF | 14 | Open-label, prospective trial | Sildenafil | 57% had a significant increase in 6MWT |
| KROWKA [72] | IPF | 51 | Phase II RCT | Inhaled iloprost | No improvement in 6MWT, NYHA class |
| JACKSON [71] | IPF | 29 | RCT | Sildenafil | No difference in 6MWT or Borg dyspnoea index score |
| ZISMAN [70] | IPF | 170 | Phase II RCT | Sildenafil | No improvement in 6MWT |
| RAGHU [73] | IPF | 220 | Phase III RCT | Ambrisentan | 6MWT/mortality. Stopped in Jan 2011: lack of efficacy and probably harm |

RCT: randomised controlled trial; iNO: inhaled nitric oxide; 6MWT: 6-minute walk test; NYHA: New York Heart Association.

However, there were a number of secondary end-points that suggested a treatment effect, including an attenuated decline in the $D_{L,CO}$ and improved preservation of quality of life measures [70]. Additionally, there was a trend towards a survival benefit in the treatment arm at 24 and 28 weeks. Subsequent *post hoc* analysis of the group of patients with echocardiographic evidence of RV dysfunction demonstrated a stronger trend toward a treatment benefit in the PH-likely subgroup of patients from this study [74].

The fourth was the Artemis PH study of ambrisentan in patients with IPF complicated by PH [73]. This study was stopped early after the Data Safety Monitoring Board overseeing the "sister" Artemis IPF study noted a trend towards worse outcomes in the treatment arm. A subgroup analysis of those patients with PH within the larger Artemis IPF study supported the notion that this group was similarly unlikely to benefit from ambrisentan. On this basis, the Artemis PH study was halted early in its recruitment phase, and no conclusion can be drawn regarding the potential effect of ambrisentan in patients with IPF and PH.

Despite these mostly disappointing results, it is still possible and indeed likely that there is a subgroup of patients with IPF and PH who may derive benefit from therapy directed at their PH. The ability to demonstrate such potential is dependent on a number of factors integral to the design and implementation of a successful study. A study primed for success will require the right agent but will also require the appropriate study duration and most importantly, the selection of a suitable patient population to meet a robust, infallible end-point. In this regard, impacting on haemodynamic indices may be meaningless without demonstrating improvements in exercise capacity, quality of life or survival.

In the absence of such studies, what are clinicians to do when faced with an IPF patient who has complicating PH? The first consideration should be to include patients in clinical trials whenever available. In the absence of such studies, a reasonable approach is to consider the use of off-label PAH medications in IPF/PH subjects on a case-by-case basis, with the proviso that patients are fully informed about the lack of supportive data and the potential risks as well as the hoped-for benefits. They should also be included in prospective PH registries [75], some of which are specifically dedicated to PH that occurs in the context of interstitial lung disease (*e.g.* the HYPID registry, NCT01443598), as these will allow unbiased evaluation of prospectively acquired data. It is our personal opinion that those patients with mild PH and a mean $P_{pa}$ lower than 30–35 mmHg probably do not warrant therapy, but that the higher the mean $P_{pa}$, the more compelling it might be to consider PAH therapies. Ideally, PH therapy should be instituted by, or in conjunction with, PH experts at tertiary centres. This is even more important when there is evidence of right heart failure and/or a diminished cardiac index that might warrant more aggressive parenteral prostanoid therapy. In treatment situations, objective goals should be decided *a priori* and, if there is no discernable objective or subjective evidence of improvement, or if oxygenation and/or exercise tolerance worsens, then consideration of treatment withdrawal should be entertained.

## Conclusion

There is a growing appreciation of PH as a common complication of IPF. It is not simply due to the progressive fibrotic process and loss of lung units, but is likely to be multifactorial in its aetiology. The reduced exercise capacity, greater oxygen requirements and reduced survival that accompany PH have raised the intriguing concept of targeted therapy with PAH agents. However, it as yet unknown whether it is the PH itself that drives the worsening outcome or whether it is a physiological correlate for other untoward parenchymal aberrations. Clinical trials in this area are therefore sorely needed and strongly encouraged to answer this fundamental question and to define those patients in whom such a treatment approach might work. Pending such studies, it is not unreasonable to consider treating patients with moderate to severe PH on a case-by-case basis in the context of full disclosure as to the potential benefits and possible risks. One only needs to be reminded of the recent IPF trials in which the therapy arms had worse outcomes (ACE, Panther and

Artemis studies) [64, 73, 76] to underline the fact that on occasion, in our quest to help, we may inadvertently impose harm with treatments that appear to make physiological and biological sense.

### *Statement of Interest*

S.D. Nathan has consulted for companies on the subject of pulmonary hypertension in idiopathic pulmonary fibrosis; these companies include Gilead, Bayer, GeNO and Ikaria. He has also received research funding from Gilead to study pulmonary hypertension in idiopathic pulmonary fibrosis. V. Cottin has received fees for speaking or consulting from Actelion, Boehringer Ingelheim, Centocor, Intermune, Lilly and Pfizer. He has also participated as an investigator in clinical trials sponsored by Actelion, Boehringer Ingelheim and Intermune, and as a member of a steering committee for a clinical trial sponsored by Boehringer Ingelheim.

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# Chapter 13

# Pulmonary hypertension in pulmonary Langerhans' cell histiocytosis

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**SUMMARY: Pulmonary Langerhans' cell histiocytosis (PLCH) is an uncommon disorder of unknown aetiology that predominantly affects young adult smokers. In patients with advanced disease, who develop airway obstruction and extensive cystic lesions on high-resolution computed tomography (HRCT), pre-capillary pulmonary hypertension (PH) is frequently observed, though no clear relationship exists between PH and extent of parenchymal lung disease and/or hypoxia. This observation suggests that alternate or additional pathomechanisms contribute to an intrinsic pulmonary vasculopathy that involves both the pre-capillary arterioles and post-capillary venous compartment, in addition to possible pulmonary veno-occlusive disease (PVOD)-like lesions.**

**Patients with PLCH who develop PH have a particularly poor prognosis and early referral for lung transplantation assessment is recommended. Encouraging recent data suggest that agents licensed for use in pulmonary arterial hypertension (PAH) (group 1 of the PH classification) confer improvements in pulmonary haemodynamics and are generally well tolerated. Further investigation into the use of medical therapy in this population is warranted.**

**KEYWORDS: Cystic lung disease, lung transplantation outcome, pulmonary hypertension, pulmonary Langerhans' cell histiocytosis**

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Pulmonary Langerhans' cell histiocytosis (PLCH) is an uncommon disease of unknown aetiology that most commonly affects young adult cigarette smokers [1, 2]. PLCH belongs to the spectrum of Langerhans' cell histiocytosis, a group of disorders characterised by the infiltration of various organs by numerous Langerhans' cells, which are often organised into granulomas [1, 2].

In adults, PLCH occurs most often as a single-system disease, and is characterised by the infiltration and destruction of the walls of distal bronchioles by Langerhans' cell granulomas [1, 2]. The natural history of the disease is widely variable. PLCH may resolve spontaneously, remain stable or progress to respiratory failure in a minority of patients [1, 2]. In patients with progressive disease, who frequently develop airway obstruction, extensive cystic lesions are the main finding on high-resolution computed tomography (HRCT) [3]. In these patients, pulmonary hypertension (PH) is a common complication that occurs several years after PLCH diagnosis in the majority of cases [4–6]. Notably, an isolated decline in diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) during the follow-up of PLCH patients should lead to investigation for the presence of PH [6].

The most recent revision of the classification system of PH identifies five different subcategories that are distinguished by virtue of their underlying pathomechanisms and clinical management [7, 8]. The fifth subcategory comprises a group of heterogeneous disorders, for which the aetiology is unclear or multifactorial [7]. PH that arises as a complication of PLCH belongs to this group [7, 8]. As is the case in several other chronic lung diseases, PH developing in the context of PLCH may be the result of chronic hypoxaemia and/or disruption of normal pulmonary biomechanics [7]. Yet a subset of patients with advanced PLCH have demonstrated markedly increased pulmonary vascular resistance (PVR) that is considered disproportionate to the extent of parenchymal lung disease [4–6]. In contrast to other parenchymal lung diseases (*e.g.* chronic pulmonary obstructive disease (COPD) and idiopathic pulmonary fibrosis (IPF)), the impairment in exercise capacity that classically affects PLCH patients is predominantly related to pulmonary vascular involvement as opposed to ventilatory limitation [9]. Indeed, a previous case series of PH complicating the course of PLCH reported a lack of correlation between lung function parameters and pulmonary haemodynamic indices, suggesting that pulmonary vascular involvement affecting PLCH patients may develop independent of the burden of parenchymal destructive lesions [4].

## Haemodynamics

In a recent report by DAURIAT *et al.* [10], 92% of 36 patients with PLCH referred for lung transplantation had PH as confirmed by right heart catheterisation (RHC), with a mean pulmonary arterial pressure ($P_{pa}$) above 35 mmHg detected in 72.5% of cases. This observation is consistent with results from previous investigators, who found that 44–100% of PLCH patients referred for lung transplantation had a mean $P_{pa}$ of 35 mmHg or over [4, 10]. Moreover, disproportionate PH may develop in patients who do not have evidence of end-stage pulmonary disease, as suggested by findings from a study by CHAOWALIT *et al.* [11] who evaluated 17 symptomatic PLCH patients from a retrospective cohort of 123 patients using transthoracic echocardiography (TTE). These authors found an estimated systolic pulmonary arterial pressure ($sP_{pa}$) above 35 mmHg in 13 (76.5%) cases and $sP_{pa}$ above 65 mmHg in seven patients. Although the exact prevalence of severe PH in PLCH patients remains unknown, these data indicate that it is likely to occur more frequently than in other chronic lung diseases that comprise group 3 of the updated PH classification (PH related to chronic lung diseases and/or hypoxia) [4, 7, 8].

## Histopathology

The typical histopathological findings of PH arising in the setting of PLCH are a severe diffuse pulmonary vasculopathy that predominantly involves the intralobular pulmonary venous compartment and, to a lesser extent, muscular pulmonary arteries (fig. 1) [4]. Although extensive pulmonary vascular involvement is typical in this form of PH, small-vessel infiltration by Langerhans' cell granulomas is rarely observed. Indeed, we observed this latter finding in only one out of 12 patients with severe PH in our initial case series [4]. The usual findings are a proliferative arteriopathy and intimal fibrosis involving small- to medium-sized pulmonary arteries in addition to intimal fibrosis and medial hypertrophy of septal veins. Notably, up to one-third of patients show a typical veno-occlusive pattern [4]. Interestingly, pulmonary vascular involvement is also

frequently observed in regions without parenchymal lesions [4, 13]. FARTOUKH *et al.* [4] found evidence from histopathological assessment of lung tissue samples examined prior to and following establishment of PH that progression of pulmonary vascular involvement occurs independently of progression of parenchymal involvement. Taken together, these observations indicate that a severe intrinsic vasculopathy that affects both the arterial and venous compartments of the pulmonary vascular tree is typical of end-stage PLCH, and these vascular changes may develop irrespective of the severity of lung parenchymal injury.

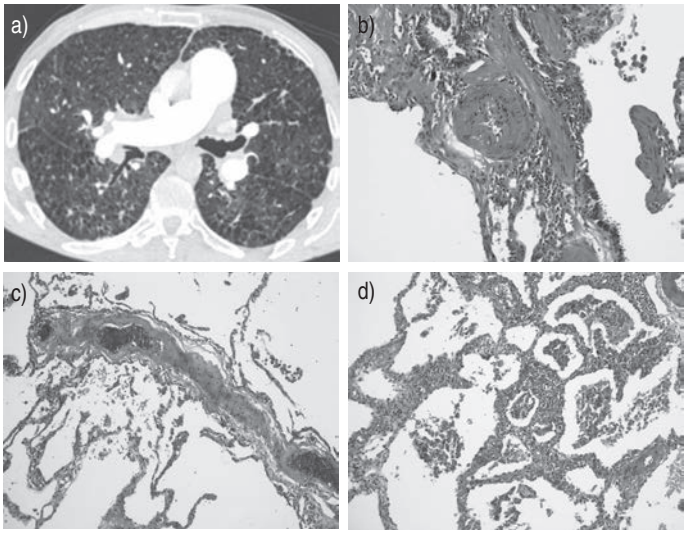


**Figure 1.** High-resolution computed tomography (HRCT) of the chest and pathological assessment of a patient with pulmonary hypertension associated with pulmonary Langherhans' cell histiocytosis. a) HRCT of the chest showing multiple small cysts and nodules. Pulmonary arterial remodelling and venous remodelling may be present in the lungs of patients suffering from this disease. b) Intimal concentric thickening of a small pulmonary artery. Magnification 200×; haematoxylin and eosin staining. c) Intimal fibrosis of a septal vein with partial obliteration. Magnification 100×; haematoxylin and eosin staining. d) When vein remodelling is present, small foci of alveolar capillary multiplication can be observed. Magnification 100×; haematoxylin and eosin staining. Reproduced from [12] with permission from the publisher.

## Prognosis

Severe PH appears to be a major determinant of outcome in PLCH patients [11, 12, 14]. The median survival following diagnosis of PH ranges from 7.6 months to over 4 years, though different criteria have been employed to define PH in previous studies [11, 14]. We have recently reported that functional impairment, as assessed using the modified New York Heart Association (NYHA) functional classification, is a powerful prognostic factor in this population of PLCH patients [6].

## Management

There is no currently approved therapy for PH that develops in the context of PLCH. Immunosuppressive therapies and/or corticosteroids have been employed in this setting, though there is no convincing evidence to support this strategy. BENYOUNES *et al.* [15] reported an initially favourable outcome with use of corticosteroids in a single patient with PH and PLCH, but this individual subsequently underwent lung transplantation for progressive disease at our centre. Another patient with PLCH and confirmed pulmonary veno-occlusive disease (PVOD) failed to improve despite prolonged corticosteroid treatment and succumbed to right ventricular (RV) failure [13]. Thus, lung transplantation remains the treatment of choice for end-stage PLCH, especially among patients with severe PH. In a multicentre, retrospective French study that examined outcomes of 39 patients undergoing transplantation (single lung, double lung or combined heart and lung) for end-stage PLCH, the 5-year survival was 57.2%. The prevalence of PH in this population was 92%. Notably, recurrence of PLCH in the graft occurred in 20% of cases in this series, though this did not impact on post-operative survival in this study and developed predominantly in those with pre-existing extrapulmonary involvement [10].

The advent of targeted medical therapies has transformed the clinical management of pulmonary arterial hypertension (PAH) (group 1 of the PH classification). In this particular PH subgroup, these agents confer significant improvements in patient symptoms, exercise capacity and

pulmonary haemodynamics. Several authors have now suggested these treatments might confer benefits in PH complicating PLCH [4, 6, 11, 13, 16]. However, caution should be exercised before this strategy is broadly recommended, particularly because of the high frequency of PVOD-like lesions. In this setting, use of medical therapies approved for PAH (group 1 of the updated PH classification) has been associated with the development of severe acute pulmonary oedema, particularly in PLCH patients treated with intravenous epoprostenol [4]. Nevertheless, a recently reported case of a PLCH patient with severe PH who demonstrated long-term improvement following treatment with the dual endothelin receptor antagonist (ERA) bosentan, thereby obviating the need for lung transplantation, demonstrates that in certain carefully selected cases this class of agent may have a therapeutic role [16]. In a recent case series, 29 consecutive PLCH patients with PH confirmed by RHC were studied. Use of PAH therapy in 12 patients was associated with significant improvements between baseline and follow-up evaluations in both mean $P_{pa}$ (from $56\pm14$ to $45\pm12$ mmHg, $p=0.03$) and PVR (from $701\pm239$ to $469\pm210$ dyn·s·cm$^{-5}$, $p=0.01$) [6]. Importantly, these haemodynamic improvements occurred without significant impact on arterial oxygen saturation ($S_{a,O_2}$) levels. Indeed, use of vasodilators in PH related to chronic respiratory diseases may lead to improvement in pulmonary haemodynamic indices, but this may occur at the expense of worsening gas exchange because of inhibition of hypoxic pulmonary vasoconstriction mechanisms and worsening of ventilation/perfusion ($V'/Q'$) mismatching [17, 18]. Furthermore, in the study by LE PAVEC *et al.* [6], there were no documented episodes of pulmonary oedema among the cohort of patients treated with ERAs, phosphodiesterase type-5 inhibitors (PDE-5 I) or inhaled prostacyclin. 1-, 3- and 5-year survival estimates of the 29 patients were 96%, 92% and 73%, respectively. NYHA functional class was the only variable significantly associated with death, with a trend toward improved survival in those patients who received PAH-specific therapies. Although these data are encouraging and suggest this management approach may have a potential role in the treatment of PLCH associated with PH, well-designed studies are required to determine the benefit/risk ratio of specific PAH therapies in this unique patient population.

## Conclusion

Pulmonary vascular involvement in the form of severe pre-capillary PH may be observed in patients with PLCH and often portends a particularly poor prognosis. Lung transplantation remains the treatment of choice for PLCH patients with severe PH. Recent case series indicate that PAH-specific therapies should be tested as a bridge or an alternative to lung transplantation in randomised clinical trials.

### *Statement of Interest*

D. Montani has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Lilly, Novartis, Pfizer and United Therapeutics. In addition to being an investigator in trials involving these companies, his relationships include consultancy services and membership of scientific advisory boards. P. Dorfmüller has participated as a speaker during a bi-annual workshop organised by Actelion and has served as a project-related consultant to Pfizer. D.S. O'Callaghan has relationships with drug companies including AstraZeneca, Boeringher, Lilly, Novartis and Pfizer (speaker's fees and/or funding for attendance at international congresses). M. Humbert has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergènes, TEVA and United Therapeutics. In addition to being investigator in trials involving these companies, his relationships include consultancy services and membership of scientific advisory boards. A. Tazi has received payments for lectures from MSD and GILEAD, and his travel to the ATS and ERS Congresses was funded by MSD and AstraZeneca.

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# Chapter 14

# Pulmonary hypertension associated with sarcoidosis

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**SUMMARY: Pulmonary hypertension (PH) affects approximately 6% of unselected patients with sarcoidosis but its prevalence is much higher in advanced pulmonary fibrosis. Although destruction of the distal capillary bed and resultant hypoxaemia are central, the underlying mechanisms are multifactorial: left heart dysfunction, specific pulmonary vasculopathy (which can cause pulmonary veno-occlusive disease), local increased vasoreactivity, extrinsic vascular compression and portal hypertension. As a result, some patients exhibit "disproportionate" PH, *i.e.* more severe than expected from the level of functional impairment. There is no validated screening algorithm for the detection of sarcoidosis-associated PH but recent studies have underlined the role of right heart catheterisation (RHC) to exclude post-capillary PH, which is frequently underestimated by echocardiography. PH is associated with a significantly increased morbidity and mortality in sarcoidosis. The cornerstone of management is supportive therapy and lung transplantation in otherwise eligible patients. Rare cases with nonfibrotic pulmonary disease respond to corticosteroids. Published data on the efficacy and safety of pulmonary arterial hypertension (PAH) agents are scarce and discrepant, requiring further studies.**

**KEYWORDS: Pulmonary hypertension, pulmonary veno-occlusive disease, sarcoidosis**

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Sarcoidosis is a multisystemic disorder of unknown aetiology characterised by the formation of immune granulomas in affected tissues, particularly the lung and lymphatic system. The disease has an estimated annual incidence of one to 40 cases per 100,000 and mainly affects people aged 25–40 years, with a predilection for female sex and black ethnicity. Multiple phenotypes are seen according to presentation, the organs involved, disease duration and severity [1]. Sarcoidosis resolves spontaneously within 2 years in half of cases and 5 years in many others. After 5 years, remission is much less probable. This difference in outcome has led us to classify patients as acute

($\leqslant$2 years) or chronic (3–5 years or more). A major concern with chronic sarcoidosis is the development of pulmonary fibrosis [1].

Pulmonary hypertension (PH) is a serious complication of sarcoidosis (sarcoidosis-associated PH), the frequency of which largely depends on the severity of pulmonary involvement. However, PH can occur at all stages of disease advancement and its underlying mechanisms are various. PH results in substantial morbidity and adversely impacts on the survival of affected patients. Over the last few years, there has been a dramatic resurgence of interest in sarcoidosis-associated PH, improving our understanding of its pathogenesis, and providing a better estimation of its prevalence and prognosis. In parallel, several studies have been conducted with new agents approved for pulmonary arterial hypertension (PAH).

This chapter examines the current literature regarding sarcoidosis-associated PH, with an emphasis on the most recent insights, including therapeutic management.

## Classification of PH and the concept of "out-of-proportion" PH

PH is defined as an increased mean pulmonary artery pressure ($P_{pa}$) of $\geqslant$25 mmHg at rest on right heart catheterisation (RHC). In an attempt to assist physicians in clinical practice, an updated clinical classification of PH derived from the Dana Point meeting was published in 2009 (see chapter 2 of this issue) [2, 3]. Group 3 of this classification is "PH due to lung diseases and/or hypoxia", including interstitial lung diseases (ILDs). Group 5 is "PH with unclear and/or multifactorial mechanisms", including sarcoidosis. This distinction from group 3 is justified by the pathogenesis of sarcoidosis-associated PH, which is much more complex than parenchymal disease and resultant hypoxia. Another important point of the new classification is that pulmonary veno-occlusive disease (PVOD) has been separated from pulmonary arterial hypertension (PAH) and classified in its own group (group 1′) [2]. However, several authors continue to consider PVOD a syndrome rather than a disease entity.

In patients suffering from ILDs, PH has long been believed to be due to the loss of capillaries in fibrotic zones and hypoxic vasoconstriction, with mean $P_{pa}$ rarely exceeding 35–40 mmHg [2, 4]. However, the concept of "out-of-proportion" PH has been the subject of growing attention in ILDs, particularly in sarcoidosis. Actually, a proportion of patients with ILD-PH sometimes exhibit out-of-proportion PH, *i.e.* a mean $P_{pa}$ >40 mmHg, which seems insufficiently explained by lung mechanical disturbances and corroborates the possible role of other underlying mechanisms, including intrinsic vasculopathy.

## Frequency of sarcoidosis-associated PH

The exact prevalence of PH complicating sarcoidosis remains to be established. The wide distribution in published rates is most probably due to the use of different measurement techniques, selection of diverse patient populations or different stages of disease (table 1). Overall, PH affects 1–6% of patients with sarcoidosis [5, 7, 9–11] but it is much more frequent in advanced lung disease [6] and symptomatic patients [12].

The only available prospective study, conducted by HANDA *et al.* [7], evaluated 212 consecutive outpatients with sarcoidosis by transthoracic echocardiography (TTE). An estimated systolic $P_{pa}$ >40 mmHg was found in 5.7% of patients. Regrettably, RHC was not performed to confirm the diagnosis of PH [7]. SHORR *et al.* [6] retrospectively reviewed a US cohort of 363 sarcoidosis patients listed for lung transplantation who had completed RHC. PH was identified in 73.8% of cases and mean $P_{pa}$ was >40 mmHg in 36.1% of patients [10]. In a retrospective study by BAUGHMAN *et al.* [8], 130 patients with persistent dyspnoea despite systemic therapy for their sarcoidosis were systematically explored with RHC; 38.5% had evidence of PH.

**Table 1.** Main studies on the prevalence of pulmonary hypertension in patients with sarcoidosis

| First author [ref.] | Population | Method | Definition | Prevalence |
|---|---|---|---|---|
| **RIZZATO [5]** | n=50<br>Methods of selection not available<br>Stage: 0, n=5; I, n=5; II, n=16; III: n=24[#] | RHC at rest, n=50<br>RHC at exercise, n=34 | Resting mean $P_{pa}$ >25 mmHg<br>Exercise mean $P_{pa}$ >30 mmHg | 3/50 (6%)<br>9/34 (26.5%) |
| **SHORR [6]** | n=363<br>Retrospective registry of patients listed for OLT | RHC at rest | Mean $P_{pa}$ >25 mmHg<br>Mean $P_{pa}$ ⩾40 mmHg | 73.8%<br>36% |
| **HANDA [7]** | 246 consecutive outpatients<br>Prospective, observational<br>Stage: 0, n=96; I, n=52; II, n=26; III, n=31; IV, n=7 | TTE peak TRJV measurable in 212 patients | Systolic $P_{pa}$ ⩾40 mmHg | 5.7% |
| **BAUGHMAN [8]** | 130 patients with persistent dyspnoea despite systemic therapy<br>Retrospective | RHC at rest | Mean $P_{pa}$ >25 mmHg with $P_{pcw}$ <15 mmHg<br>Mean $P_{pa}$ ⩾40 mmHg<br>$P_{pcw}$ ⩾15 mmHg | 50/130 (38.5%)<br>14/130 (10.8%)<br>20/130 (15.4%) |

OLT: orthotoptic lung transplantation; RHC: right heart catheterisation; TTE: transthoracic echocardiography; TRJV: tricuspid regurgitation jet velocity; $P_{pa}$: pulmonary artery pressure; $P_{pcw}$: pulmonary capillary wedge pressure. [#]: stage III included patients with or without fibrosis.

No difference has been observed between patients with and without PH in terms of sarcoidosis phenotype or demographic characteristics, except for a higher frequency of stage IV disease on chest radiography [7, 8, 13–15] and possible male predominance [7].

## Pathogenesis of sarcoidosis-associated PH

As already indicated, sarcoidosis is classified in group 5 of the Dana Point PH classification but, essentially, the mechanisms of sarcoidosis-associated PH may fit into all five groups [2, 4].

### Pre-capillary PH

#### *Destruction of the distal capillary bed and resultant hypoxaemia*

The majority of sarcoidosis patients with PH have evidence of advanced disease [7, 8, 13–15]. However, 31.8% to 50% of patients with sarcoidosis-associated PH develop this complication in the absence of patent pulmonary fibrosis [8, 14, 15] and a small subset of cases have no apparent underlying lung disease (radiographic stage 0–I) [7, 8, 14–16]. Moreover, haemodynamic measurements do not correlate well with spirometric parameters and arterial oxygen tension ($P_{a,O_2}$) [7, 12, 14, 17], and mean $P_{pa}$ is 9 mmHg higher in sarcoidosis than in idiopathic pulmonary fibrosis (IPF) for equivalent levels of respiratory impairment (34.4 *versus* 25.6 mmHg, $p<0.0001$) [18]. Finally, the degree of PH is sometimes disproportionate to functional abnormalities [6, 8, 14, 19] and PH may even be more severe when it occurs in patients without fibrotic disease [14]. Taken together, these findings support the idea that other mechanisms may play a role in the development of sarcoidosis-associated PH. These include specific vasculopathy, locally increased vasoreactivity, extrinsic compression of pulmonary vessels, left heart dysfunction and portal hypertension. Comorbidities associated with sarcoidosis can also cause PH.

### *Specific vasculopathy*

Vascular involvement is very common in pulmonary sarcoidosis, occurring in 69–100% of cases according to pathological studies [20, 21]. Changes consist of occlusive or destructive lesions due to the invasion of vessel walls by granulomas or to perivascular fibrosis [20, 21]. Vascular involvement can be observed at all levels, from large branches of the pulmonary artery to small veins, but it prevails in the venous side, reflecting the lymphatic spreading of the granulomatous process (figs 1 and 2) [20–22]. Despite frequent granulomatous vascular involvement, clinically significant PH is rare. In the autopsy study by TAKEMURA *et al.* [21], significant PH was noted in only four out of 40 patients with vascular involvement. The reasons why some individuals will develop PH are not completely understood.

PVOD-like disease is now a well-recognised cause of sarcoidosis-associated PH [14, 23, 24]. The occlusive narrowing of interlobular veins by granulomas can mimic PVOD and result in PH. This mechanical granulomatous PVOD has been pathologically authenticated in a handful of cases with nonfibrotic sarcoidosis [23, 24]. In addition, NUNES *et al.* [14] described an intrinsic occlusive venopathy in explanted lungs from five sarcoidosis patients with PH and pulmonary fibrosis. This venopathy was characterised by marked intimal fibrosis and recanalisation of the interlobular septal veins associated with chronic haemosiderosis. Conversely, arterial changes were minor with no evidence of plexiform or thrombotic lesions. Scattered granulomas were present in the veins of four out of five cases whereas arterial granulomas were seen in only two cases and neither venous nor arterial granulomas were found in one patient [14]. Interestingly, a similar venopathy has also been described in another "granulomatous" disorder, pulmonary Langerhans' cell histiocytosis (PLCH) [25].

### *Locally increased vasoreactivity*

The potential role of heightened reactivity of the pulmonary vasculature to vasoactive mediators has been raised because a number of patients with sarcoidosis-associated PH are responders to acute vasodilator challenge with inhaled nitric oxide or prostacyclin [19, 26, 27]. Among the various contenders, endothelin-1 (ET-1) is the most attractive. ET-1 is a potent vasoconstrictive cytokine, which also possesses pro-inflammatory and mitogenic properties, in particular for smooth muscle cells and fibroblasts, inducing vascular remodelling. Yet, despite emerging results, data are currently limited and no study has compared ET-1 measurements with the presence of PH.

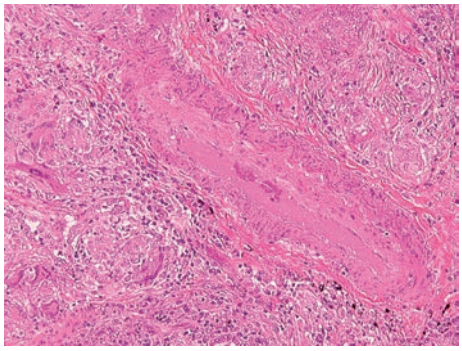

**Figure 1.** Pulmonary arterial involvement of sarcoidosis. Coalescent granulomas adjacent to the adventitia of an intralobular artery, which narrow the vascular lumen. Haematoxylin and eosin staining. Magnification ×100.

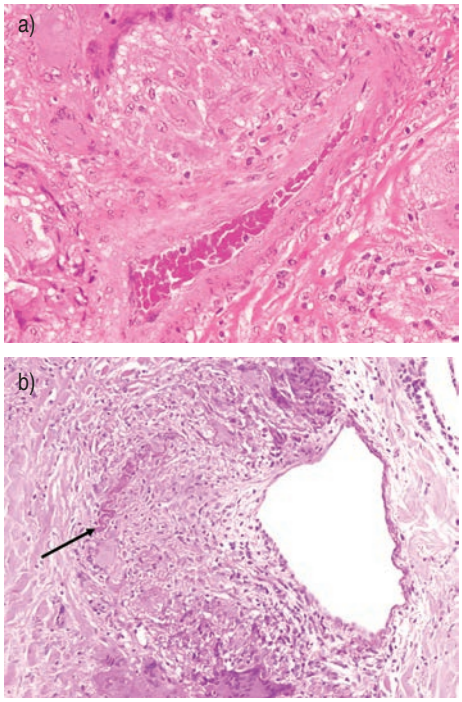


**Figure 2.** Pulmonary venous involvement of sarcoidosis. a) Granulomas in the wall of an interlobular vein, with a partial occlusion of the vascular lumen. b) Invasion of the venous wall by fibrotic granulomas, which results in hemi-circumferential destruction, with a disruption of the elastic laminae (arrow) and vascular luminal narrowing. Haematoxylin and eosin staining. Magnification ×100.

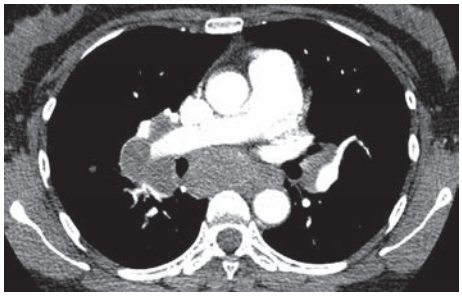

**Figure 3.** High-resolution computed tomography of the lungs of a patient with sarcoidosis-associated pulmonary hypertension and vascular extrinsic compression by lymphadenopathies. Multiple lymph nodes with an extrinsic compression of the right main pulmonary artery and a slightly increased calibre of the pulmonary trunk compared with the aorta are seen.

SOFIA *et al.* [28] demonstrated that urine but not plasma levels of ET-1 were significantly higher in sarcoidosis than in IPF. Urine ET-1 decreased significantly in sarcoidosis patients receiving corticosteroids, and the decrease concurred with clinical improvement. Urine ET-1 was significantly correlated with the intensity of lymphocytic alveolitis [28]. Conversely, plasma ET-1 was increased in sarcoidosis patients compared with healthy controls in the study by LETIZIA *et al.* [29]. In those who went into remission following successful corticosteroid therapy, ET-1 levels normalised in parallel with other parameters of disease activity [29]. REICHENBERGER *et al.* [30] examined ET-1 concentrations in bronchoalveolar lavage (BAL) specimens from patients with various pulmonary disorders and healthy controls. Elevated ET-1 levels were observed in sarcoidosis patients, which were comparable to those seen in scleroderma and IPF patients [30, 31]. BAL ET-1 was also compared between 22 nonsmoking sarcoidosis patients and 12 nonsmoking healthy controls in the study by TERASHITA *et al.* [31]. Levels were significantly higher in sarcoidosis and they were correlated with the number of alveolar macrophages harvested in BAL. Similarly, ET-1 immunoreactivity was localised mainly in alveolar macrophages. Lastly, BAL fluid (BALF) from the sarcoidosis patients stimulated fibroblast proliferation, compared with control BALF, and fibroblast proliferation was blocked in the presence of an ET-1 inhibitor [31]. Consistent with this, earlier work had demonstrated that alveolar macrophages from sarcoidosis patients were a primary source of ET-1, and that the supernatant from these alveolar macrophages incited the growth of fibroblasts [32].

### *Extrinsic compression of pulmonary vessels*

Sarcoidosis-associated PH may be caused by extrinsic compression of the proximal pulmonary artery by enlarged lymph nodes or fibrosing mediastinitis (fig. 3) [14, 33, 34]. Compression of the large pulmonary veins is much rarer and can provoke localised oedema. Although occasionally described in early stages of sarcoidosis, pulmonary artery compression is much more frequent in patients with long-standing disease when lymph nodes become fibrotic and calcify. This mechanism was demonstrated in 21.4% of patients with PH and radiographic stage IV sarcoidosis in the study of NUNES *et al.* [14].

### *Portal hypertension*

PH may also be the consequence of hepatic sarcoidosis, which can rarely lead to cirrhosis and portal hypertension [35].

## Post-capillary PH

Clinical myocardial involvement is seen in about 5% of sarcoidosis patients and can generate left ventricular (LV) systolic or diastolic impairment. Notably, unsuspected occult involvement is much more frequently revealed by pathological examination [36]. Several Doppler echocardiographic studies have pointed to a high prevalence of diastolic dysfunction (14–50%) in patients without clinical evidence of cardiomyopathy, possibly mirroring early cardiac disease [37, 38]. Similarly, in sarcoidosis patients awaiting lung transplantation, although within normal values for the vast majority of patients, pulmonary capillary wedge pressure ($P_{pcw}$) is, on average, significantly higher in the presence of PH and it is also independently associated with PH, which indicates that subtle impairment in cardiac diastolic performance may nonetheless exist [6].

Although newer techniques have improved the detection of LV dysfunction in sarcoidosis [36], the reliability of routine TTE is weak in such a context. The study by BAUGHMAN *et al.* [8] cited earlier

in this chapter is extremely interesting in this regard. 130 sarcoidosis patients with persistent dyspnoea were thoroughly investigated by RHC [8]. LV dysfunction, defined as an elevated $P_{pcw}$, was revealed in 20 (15.4%) subjects, which represented 28.6% of all cases with PH [8]. Only seven (35%) of them had a reduced LV ejection fraction on TTE [8].

### Comorbidities

A potential link between sarcoidosis and thromboembolic events has recently been emphasised [39, 40]. CRAWSHAW *et al.* [39] performed a retrospective cohort analysis using a well-established epidemiological data set, covering the period between 1963 and 1998, which recorded all hospital admissions to National Health Service hospitals and all deaths in Oxfordshire, UK. A significant association was demonstrated between sarcoidosis and pulmonary embolism, in comparison with a matched reference population (OR 1.92, 95% CI 1.05–3.23; $p=0.01$), but not deep-vein thrombosis [39]. Using US death certificates from 1988 to 2007, SWIGRIS *et al.* [40] showed that pulmonary embolism was declared for 2.54% of decedents with sarcoidosis, compared with only 1.13% of the background population (OR 2.3, 95% CI 2.1–2.5; $p<0.0001$). The risk was significantly greater than for descedents with chronic obstructive pulmonary disease (COPD) [40]. However, to the best of our knowledge, post-embolic PH has been described only in unique patients with sarcoidosis showing exuberant granulomas inside the thrombi at pathology [41].

The reasons why sarcoidosis confers an increased risk for pulmonary embolism remain to be elucidated. The rate of either antiphospholipid immunoglobulin (Ig)G or IgM in sera reached 38% of sarcoidosis patients in the study of INA *et al.* [42], which was significantly more than in healthy controls. Several observations have described antiphospholipid syndrome occurring in sarcoidosis patients with [43] or without concomitant lupus [44, 45]. In addition, sarcoidosis can co-exist with various autoimmune disorders known to facilitate thromboembolic disease and/or PAH, including Takayasu arteritis [46] and systemic scleroderma [47].

Lastly, a higher than expected prevalence of obstructive sleep apnoea (OSA) has been observed in sarcoidosis [48, 49], attaining 17% in one study [48].

## Diagnosis of sarcoidosis-associated PH

The clinical picture of an underlying respiratory disorder can mask PH and delay its recognition. However, several symptoms should prompt diagnostic intervention: dyspnoea more severe than one would expect from functional impairment; chest pain; palpitations; and near-syncope on exertion. Physical signs include: a loud $P_2$ component to the second heart sound; a fixed, split $S_2$; a holosystolic murmur of tricuspid regurgitation; and a diastolic murmur of pulmonic regurgitation. About one-quarter of patients with sarcoidosis-associated PH present with signs of right-sided heart failure [14, 15]. Raynaud's phenomenon is occasionally noted as in idiopathic PAH (IPAH) [14]. ECG may show signs of right ventricular (RV) strain and chest radiography may show right cardiomegaly and pulmonary artery enlargement.

### Transthoracic echocardiography

Admittedly, TTE is an imperfect diagnostic method, but it remains the most appropriate modality for the noninvasive assessment of PH. In ILDs, the peak velocity of the tricuspid regurgitant jet is measurable in only 44–54% of patients and, even if available, estimation of the systolic $P_{pa}$ is often inaccurate [50–52]. ARCASOY *et al.* [50] examined the performance of TTE in 106 patients with diverse forms of ILDs referred for lung transplantation, using RHC as the gold standard. Despite the significantly higher likelihood of achieving an estimation of systolic $P_{pa}$ in ILDs, the accuracy of TTE was much worse than in COPD. There was a good correlation between systolic $P_{pa}$ estimated by TTE and that measured by RHC but the values were within 10 mmHg in only 37% of patients with ILDs. When considering estimated systolic $P_{pa}$ in excess of 45 mmHg as a

determinant of PH, the sensitivity, specificity, and positive and negative predictive values of TTE were 85%, 17%, 60% and 44%, respectively. When RV abnormalities were used as a surrogate diagnostic marker of PH, the values for TTE were 76%, 53%, 57% and 74%, respectively [50]. Unfortunately, there is little specific information for sarcoidosis available [8, 13]. In the study by BAUGHMAN *et al.* [8], 80 patients underwent both echocardiographic and haemodynamic assessments. Of these, only 70% had sufficient tricuspid regurgitant jet identified such that systolic $P_{pa}$ could be estimated. For these cases, there was a significant correlation between estimated and measured systolic $P_{pa}$ ($r=0.62$, $p<0.0001$). Sensitivity and specificity of TTE were not reported in this study [8].

Hence, the absence of an increased systolic $P_{pa}$ appears to be suboptimal to exclude significant PH and does not obviate the need for RHC in selected patients. RV abnormalities are valuable additional parameters to reinforce suspicion of PH, irrespective of tricuspid regurgitant velocity.

## Right heart catheterisation

Although definite diagnosis relies on invasive measurements, not all patients with ILDs and suspected PH should undergo confirmatory RHC. The European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines assert the following reasonable indications for RHC in group 3 PH: 1) proper diagnosis of PH in candidates for transplantation; 2) suspected out-of-proportion PH potentially amenable to enrolment in a clinical trial with specific PAH drug therapy; 3) frequent episodes of right heart failure; and 4) inconclusive echocardiographic study in cases with a high index of clinical suspicion [4]. In sarcoidosis, a wider adoption of RHC has, however, gained credit following the published experience of BAUGHMAN and co-workers [8, 12]. As discussed previously, left-heart dysfunction is not uncommon in sarcoidosis and probably underrated by TTE [8]. Furthermore, RHC also provides important information on prognosis [8, 53, 54]: on the one hand, it allows assessment of the severity of haemodynamic impairment; on the other, the pre- or post-capillary nature of PH has not only therapeutic but also prognostic implications [8].

The haemodynamic severity of sarcoidosis-associated PH is extremely variable. In the study by BAUGHMAN *et al.* [8] on 50 patients with pre-capillary PH, median mean $P_{pa}$ was 33 mmHg (range 25–75 mmHg) and median pulmonary vascular resistance (PVR) was 4.3 Wood units (range 0.9–21.2 Wood units). These patients displayed a similar mean $P_{pa}$ but a significantly higher PVR than those with PH due to LV dysfunction. Mean $P_{pa}$ was over 35 and 40 mmHg in 46% and 28% of patients with pre-capillary PH, respectively [8]. Out-of-proportion PH seems more frequent in patients without than with pulmonary fibrosis [6, 14]. As therapy with high doses of calcium channel blockers (CCBs) has no role in group 3 PH, acute vasodilator challenge is not recommended in the majority of patients with ILDs but may still be useful for some with sarcoidosis. The rate of patients with a positive short-term response varied between 0% and 87.5% in three series [14, 19, 26, 27], depending on the agent used and the definition of response.

## Pulmonary function tests and the 6-minute walk test

Most studies have shown statistically lower forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), total lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) values in sarcoidosis patients with PH [7, 8, 13–15]. These patients are also more hypoxaemic and/or require more frequent supplemental oxygen than those without PH [6, 7, 8, 13–15]. Nonetheless, the contribution of pulmonary function tests (PFTs) alone for the identification of patients with PH is modest. In multivariate analysis, the need for oxygen remained the only predictor of PH in the transplant cohort of SHORR *et al.* [6] (OR 8.39, 95% CI 3.44–20.47), with a sensitivity and specificity of 91.8% and 32.6%, respectively. In other words, relying on oxygen requirement would lead to the misclassification of nearly one-third of patients in this population [6]. HANDA *et al.* [7] demonstrated that only decreased

TLC was independently associated with echocardiographic PH in consecutive outpatients with sarcoidosis (OR 0.69, 95% CI 0.48–0.99; $p<0.05$) but its predictive power was mild. Because the reduction of $D_{L,CO}$ can be related to both interstitial and vascular involvement, several authors have postulated that a high FVC/$D_{L,CO}$ ratio (with a cut-off of 1.4–1.5), reflecting a disproportionately reduced $D_{L,CO}$ for the degree of restriction, may be a better tool for gauging PH in ILDs, alone or together with arterial oxygen saturation ($S_{a,O_2}$) [55–59]. The ability of the FVC/$D_{L,CO}$ ratio to screen for PH has never been tested in sarcoidosis, although findings are significantly higher in patients with increased echocardiographic systolic $P_{pa}$ (mean ± SD 1.6 ± 0.7 *versus* 1.2 ± 0.4, $p<0.01$) [15]. No study has focused on the predictive value of the measure of membrane and blood components of $D_{L,CO}$ for the detection of PH in sarcoidosis.

BAUGHMAN *et al.* [60] prospectively evaluated the 6-minute walk test (6MWT) in 142 sarcoidosis patients. The 14 patients with documented PH accomplished a significantly shorter distance, with a median of 280 m *versus* 411 m for all other patients [60]. Similar results were found in the retrospective study of BOURBONNAIS *et al.* [13] on 162 patients, which aimed to determine the clinical predictors of PH in sarcoidosis. The 22 patients with PH walked shorter distances (343 ± 116 *versus* 426 ± 105 m, $p<0.004$) and had greater desaturation (8.85 ± 4.22% *versus* 2.99 ± 2.14%, $p<0.001$) and Borg score at 6 minutes [13]. After adjusting for body mass index (BMI) and age, multivariate analyses showed that the significant predictors of PH on TTE were $S_{a,O_2}$ <90% on 6MWT (OR 12.1, 95% CI 3.66–19.73) and $D_{L,CO}$ <60% predicted (OR 7.3, 95% CI 1.98–24.82). $D_{L,CO}$ did not retain significance when PH was defined using RHC. These cut-off values for $S_{a,O_2}$ and $D_{L,CO}$ were obtained from the receiver operating characteristic (ROC) curves. The other variables tested, including 6MWT distance and all other PFT parameters, failed to predict the presence of PH. Interestingly, all seven patients being misdiagnosed as having no PH on TTE desaturated to <90% during the 6MWT, suggesting that a composite model combining the results of $S_{a,O_2}$ on 6MWT with those of TTE would improve the pre-test probability before performing RHC [13]. Although not clearly evaluated, exercise testing may be interesting to identify PH in patients with ILDs, in particular sarcoidosis.

## Imaging

Contrast-enhanced high-resolution computed tomography (HRCT) can show an increased pulmonary artery calibre (widest diameter of the main pulmonary artery >29 mm or greater than that of the ascending aorta). Even so, the pulmonary artery diameter and pulmonary artery/aorta ratio are not reliable for predicting the presence of PH in ILDs [61, 62], possibly because the restrictive lung physiology may result in a traction effect on the mediastinal vascular structures, distending the pulmonary artery independently of the underlying $P_{pa}$. In sarcoidosis, contrast-enhanced HRCT helps delineate the mechanisms of PH. First, it allows the diagnosis of extrinsic vascular compression (fig. 3). Secondly, several findings may hint at PVOD, such as extensive ground-glass opacities and/or thickened interlobular septa (fig. 4). Although these features may be related solely to sarcoidosis, NUNES *et al.* [14] demonstrated that patients with sarcoidosis-associated PH showed a significantly higher frequency of ground-glass attenuation and septal lines compared with sarcoidosis controls without PH. The differentiation of extrinsic vascular

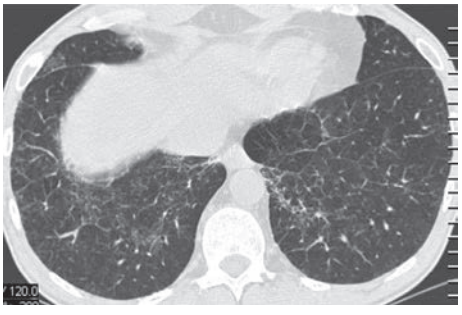

**Figure 4.** High-resolution computed tomography of the lungs of a patient with sarcoidosis-associated pulmonary hypertension and suspicion of pulmonary veno-occlusive disease. A network of septal reticulations in association with ground-glass opacities are seen, increasing the possibility of pulmonary veno-occlusive disease.

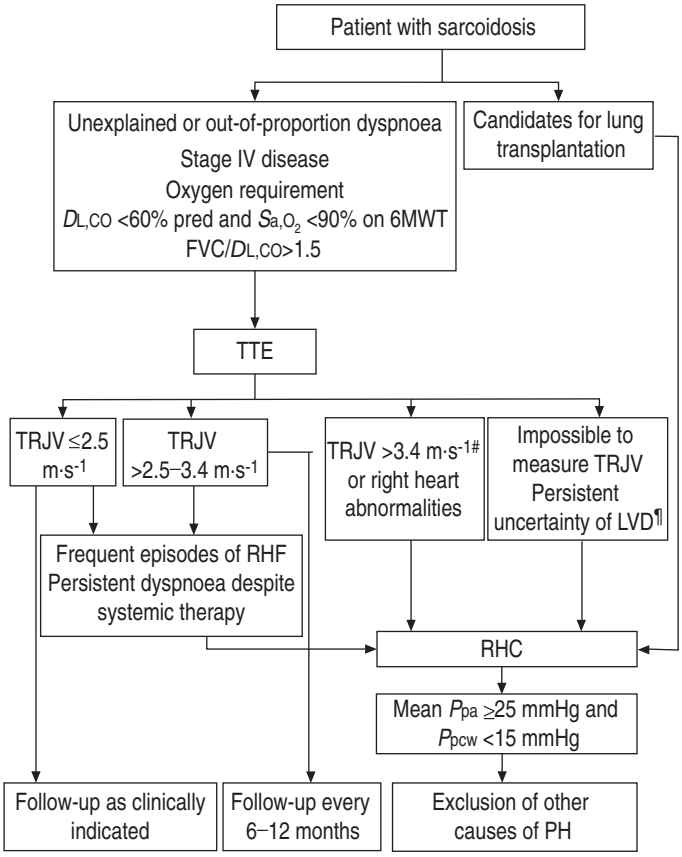
Patient with sarcoidosis
Unexplained or out-of-proportion dyspnoea
Stage IV disease
Oxygen requirement
DL,CO <60% pred and Sa,O2 <90% on 6MWT
FVC/DL,CO>1.5
Candidates for lung transplantation
TTE
TRJV ≤2.5 m·s-1
TRJV >2.5–3.4 m·s-1
TRJV >3.4 m·s-1# or right heart abnormalities
Impossible to measure TRJV Persistent uncertainty of LVD¶
Frequent episodes of RHF Persistent dyspnoea despite systemic therapy
RHC
Mean Ppa ≥25 mmHg and Ppcw <15 mmHg
Follow-up as clinically indicated
Follow-up every 6–12 months
Exclusion of other causes of PH

**Figure 5.** Proposed algorithm for the screening of sarcoidosis-associated pulmonary hypertension (PH). $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; $S_{a,O_2}$: arterial oxygen saturation; 6MWT: 6-minute walk test; FVC: forced vital capacity; TTE: transthoracic echocardiography; TRJV: tricuspid regurgitant jet velocity; LVD: left ventricular dysfunction; RHF: right heart failure; RHC: right heart catheterisation; $P_{pa}$: pulmonary artery pressure; $P_{pcw}$: pulmonary capillary wedge pressure. #: out-of-proportion PH can be suspected on TTE if TRJV >3.4 m·s$^{-1}$ (estimated systolic $P_{pa}$ >55–60 mmHg); ¶: particularly left ventricular diastolic dysfunction.

compression from pulmonary embolism is sometimes tricky and occasionally requires pulmonary angiography. Hepatic ultrasound is necessary to exclude portopulmonary hypertension (POPH).

### Natriuretic peptides

Plasma brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP may be helpful biomarkers for the detection of PH in patients with ILDs. In the study by LEUCHTE *et al.* [63] in patients with diverse ILDs, elevated plasma BNP levels were predictive of moderate-to-severe PH, defined as mean $P_{pa}$ >35 mmHg on RHC, with 100% sensitivity and 89% specificity. BNP is also independently associated with a higher risk of mortality in ILDs [64–66]. HANDA *et al.* [67] performed a prospective study of 150 consecutive sarcoidosis patients to investigate the utility of plasma NT-proBNP in the assessment of PH and cardiac involvement. Among the 130 subjects evaluable for PH status at TTE, 21 were diagnosed with PH (defined as a systolic $P_{pa}$ >35 mmHg). Patients with PH had significantly higher levels of NT-proBNP compared with those without but the increase was milder than in patients with cardiac involvement. Moreover, NT-proBNP had a poor discriminative capacity for PH, even when patients with cardiac sarcoidosis were excluded. The sensitivity and specificity were 75.0% and 60.9%, respectively, the optimal cut-off value being 103 pg·mL$^{-1}$ based on ROC curves [67].

## Screening of sarcoidosis-associated PH

As PH bears severe prognosis in sarcoidosis, early diagnosis and consideration of treatment options may be keys to improve patients' outcomes. Nonetheless, there is no consistent single clinical criterion that can be used to adequately segregate sarcoidosis patients with a high or low risk for PH. Owing to the limited accuracy of TTE, this should not serve as the only guide to determine who requires further invasive intervention. In light of recent data, RHC seems particularly important in patients with persistent uncertainty regarding LV dysfunction and/or who continue to experience dyspnoea despite systemic therapy. However, the balance of benefit, risk and costs of such a procedure has been questioned [68]. Once PH is confirmed, a comprehensive workup is intended to scrupulously rule out the other classical causes of PH, chiefly pulmonary embolism. In cases with

suspected heart sarcoidosis, several cardiac tests complement RHC. A screening algorithm for sarcoidosis-associated PH is proposed in figure 5.

## Clinical impact and prognosis of sarcoidosis-associated PH

PH is a debilitating condition in sarcoidosis patients, which accounts for refractory dyspnoea [12] and reduced exercise capacity [13, 60]. Additionally, the burden of PH on functional status and employment status is substantial [6]. Transplantation candidates with PH are more likely to need some or total assistance with their activities of daily living (nearly 70% of those with a mean $P_{pa}$ $\geqslant$40 mmHg) and PH increases the risk of being unemployed due to disease [6]. Furthermore, PH is well-known to portend a pejorative outcome [8, 14, 16, 18, 69, 70]. In sarcoidosis subjects waiting for lung transplantation, mean $P_{pa}$ is an independent predictor of death together with oxygen requirement [69, 70]. In the cohort of NARDI *et al.* [71] consisting of 142 stage IV patients originating from a nontransplant centre, the occurrence of PH was the most robust correlate of mortality, with an 8.1-fold increase in risk of death (95% CI 2.1–31.6, p=0.002), and intractable right heart failure was the primary cause of mortality (31.2%).

In the retrospective series of NUNES *et al.* [14] consisting of 22 patients with sarcoidosis-associated PH, 2- and 5-year survival rates were 73.5% and 59%, respectively, which was significantly worse than for matched controls without PH. BAUGHMAN *et al.* [8] demonstrated that the relative risk of death in the presence of PH without LV dysfunction *versus* no PH was 10.39 (95% CI 2.99–13.78, p<0.0001) and 3.14 (95% CI 1.01–5.62, p<0.05) when comparing PH without or with LV dysfunction. The median survival was 4.2 years for patients with pre-capillary PH. There was a significant difference in survival curves according to the level of PVR (<3 or $\geqslant$3 Wood units). On multivariate analysis, only two independent parameters were proven to be predictors of mortality in the studied population: stage IV radiography and presence of PH (hazard ratio 7.43, 95% CI 2.26–24.45) [8].

## Treatment of sarcoidosis-associated PH

In view of limited reports on the subject, no recommendation can be drawn on the optimal therapeutic strategy for sarcoidosis-associated PH, which should take into account the prominent underlying mechanism of PH. Obviously, supportive therapy is the cornerstone of management, including supplemental oxygen in patients who are hypoxaemic at rest or during exercise, and diuretics as needed.

With respect to therapy directed against sarcoidosis, published results are somewhat discrepant. PH has been shown both to worsen despite corticosteroids [72–76] and to improve dramatically [77, 78]. GLUSKOWSKI *et al.* [76] evaluated the effect of 12 months of corticosteroid treatment on the haemodynamics of 24 patients with pulmonary sarcoidosis, of whom three had PH at rest and 18 had PH on exercise. Whereas most patients had improvements on chest radiography and PFTs, only half showed improved haemodynamics [76]. In the study by NUNES *et al.* [14], 10 patients with sarcoidosis-associated PH received high doses of oral prednisone. This was inefficient in the five patients with stage IV but a sustained improvement was obtained in three out of the five cases without pulmonary fibrosis [14]. Interestingly, in one reported case, comparisons of subsequent specimens taken before and after established PH (open-lung biopsy and autopsy) showed a clear progression of the pulmonary vascular involvement whereas parenchymal lesions of sarcoidosis stayed relatively stable with corticosteroids [75].

There are four classes of PAH agents: 1) CCBs, which are reserved for a small subgroup of patients with positive acute vasoreactivity tests; 2) prostacyclin analogues; 3) endothelin receptor antagonists (ERAs); and 4) phosphodiesterase type-5 inhibitors (PDE-5 I) [4]. According to the ERS/ESC guidelines, the use of PAH-targeted therapy is discouraged in group 3 PH when mean $P_{pa}$ is <40 mmHg [4]. It may be proposed to patients with out-of-proportion PH in expert centres, ideally as part of randomised controlled trials [4]. There has long been concern over systemic pulmonary vasodilators leading to an aggravation of hypoxaemia, because of the

**Table 2.** Main studies on long-term pulmonary arterial hypertenaion-targeted therapy for sarcoidosis-associated pulmonary hypertension

| First author [ref.] | Patient characteristics | Agent | Effect | Outcomes |
|---|---|---|---|---|
| **PRESTON [19]** | n=7<br>Stage: III, n=1; IV, n=6<br>Baseline mean $P_{pa}$ mean ± SE 55 ± 4 mmHg<br>Baseline PVR mean ± SE 896 ± 200 dyn·s·cm$^{-5}$ | iNO, n=4<br>iNO+epoprostenol, n=1<br>CCBs, n=2 | Patients treated with iNO: improvement of 6MWD in 5/5 and NYHA FC in 3/5; worsening of haemodynamics in 3/3<br>Patients treated with CCBs: worsening in 2/2 | 6 patients died<br>2 patients alive under iNO for 1.5 and 2 years, respectively, awaiting transplantation |
| **BAUGHMAN [82]** | 15 out of 22 (7 patients could not complete 16 weeks therapy for several reasons)<br>Stage: 0, n=1; I, n=1; II, n=1; III, n=1; IV, n=11 Baseline mean $P_{pa}$ 36 (20–62) mmHg<br>Baseline PVR 488 (157–1304) dyn·s·cm$^{-5}$ | Inhaled iloprost | Patients were followed prospectively<br>At 16 weeks, 8/15 were considered responders, defined as either an increase in 6MWD ⩾30 m or a decrease in PVR ⩾ 20%<br>Globally, SGRQ activity score decreased significantly | NA |
| **FISHER [27]** | n=5<br>Stage: I, n=1; III, n=1; IV, n=3<br>Baseline mean $P_{pa}$ 58 ± 7 mmHg<br>Baseline PVR 1142 ± 568 dyn·s·cm$^{-5}$ | *i.v.* epoprostenol | Improvement in NYHA FC for all patients | 4 patients alive and 1 transplanted after an average of 29 months therapy |
| **MINAI [83]** | n=6 | *i.v.* epoprostenol, n=3<br>Bosentan, n=3 | 4 initial responders (increase in 6MWD >50 m at 3–6 months): 2 with epoprostenol and 2 with bosentan<br>Only 1 responder at 12 months | NA |
| **BAUGHMAN [12]** | n=7<br>Baseline mean $P_{pa}$ 53.4 ± 13.4 mmHg | Bosentan, n=4<br>Bosentan+epoprostenol, n=1<br>Epoprostenol, n=1<br>CCBs, n=1 | Significant improvement of haemodynamics in 4/5 (bosentan, n=2; epoprostenol, n=1; CCBs, n=1) and stability in 1/5 (CCBs) | Follow-up between 4 and 8 months<br>2 patients died |
| **MILMAN [84]** | n=12<br>Patients with end-stage disease referred for lung transplantation<br>Baseline mean $P_{pa}$ 48 ± 15 mmHg<br>Baseline PVR 856 ± 384 dyn·s·cm$^{-5}$ | Sildenafil | Treatment was given for a median duration of 4 (1–12) months<br>Significant improvement of haemodynamics in 9 tested patients (mean $P_{pa}$ -8 mmHg, PVR -392 dyn·s·cm$^{-5}$) with a decrease in PVR ⩾20% in 6/9<br>No significant change in 6MWD | NA |

**Table 2.** Continued

| First author [ref.] | Patient characteristics | Agent | Effect | Outcomes |
|---|---|---|---|---|
| **BARNETT [16]** | n=22<br>Stage: 0, n=3; II: n=3, III: n=1; IV, n=15<br>Baseline mean $P_{pa}$ 46.1±2.7 mmHg<br>Baseline PVR 810±89.1 dyn·s·cm$^{-5}$ | Initial monotherapy: Bosentan, n=12; Sildenafil, n=9; Epoprostenol, n=1<br>Various combination therapies (inadequate response to initial monotherapy), n=8 | Improvement of NYHA FC in 9 patients, significant increase in 6MWD in 18 patients (+59 m), significant improvement of haemodynamics in 12 patients (mean $P_{pa}$ -9.1 mmHg, PVR: -350 dyn·s·cm$^{-5}$)<br>Patients with higher FVC had greater increase in exercise capacity | Median of 11 months of follow-up<br>1- and 3-year transplant-free survival rates 90% and 74%, respectively |
| **JUDSON [85]** | n=21 (11 patients could not complete 24 weeks therapy for several reasons)<br>Stage: 0, n=2; I, n=0; II, n=8; III, n=2; IV, n=8<br>Baseline mean $P_{pa}$ 32.7±7.3 mmHg<br>Baseline PVR 5.9±2.3 Wood units | Ambrisentan | Patients were followed prospectively<br>Overall, at 24 weeks, no significant change in 6MWD, Borg scale, serum BNP or QoL<br>For patients who completed therapy, nonsignificant improvement of WHO-FC and SGRQ | NA |

Data are presented as median (range) or mean±SD, unless otherwise stated. All studies were retrospective, except for two prospective, open-label, uncontrolled studies [82, 85]. $P_{pa}$: pulmonary artery pressure; PVR: pulmonary vascular resistance; iNO: inhaled nitric oxide; CCB: calcium channel blocker; 6MWD: 6-minute walking distance; NYHA: New York Heart Association; FC: functional class; SGRQ: St George's Respiratory Questionnaire; FVC: forced vital capacity; BNP: brain natriuretic peptide; QoL: quality of life; WHO: World Health Organization; NA: not available.

inhibition of hypoxic pulmonary vasoconstriction with subsequent increased ventilation/perfusion mismatch and shunting. Therefore, delivery of these medications, including nitric oxide or prostanoids, to well-ventilated lung units *via* inhalation has been preferred [79]. Yet, while decreased arterial oxygenation is observed with CCBs and intravenous epoprostenol [79, 20], it is not observed with oral sildenafil (a PDE-5 I) [80] or bosentan (a dual ETA and ETB ERA) [81].

In sarcoidosis-associated PH, the intrinsic vasculopathy that exists in a subset of patients makes the use of PAH-specific agents appealing. Unfortunately, available data are scarce and results are variable. The main studies on long-term responses to PAH therapy are summarised in table 2 [12, 16, 19, 27, 82–86]. These include only two prospective uncontrolled trials [82, 85], the others being retrospective small series or case observations.

These conflicting results are confusing for clinicians and spark the need for prospective randomised, placebo-controlled trials. A more rational approach is critical to define which patients to treat (perhaps on the basis of radiographic stage and/or lung function and/or mean $P_{pa}$), which drug to prescribe and whether it should be used after immunosuppressive therapy or in association with it. In any case, these drugs should be used with caution in patients with suspected PVOD. One case of sudden death and one case of acute pulmonary oedema have been described following *i.v.* epoprostenol [27]. Clinical trials are underway to determine the efficacy and safety of PAH therapy in sarcoidosis-associated PH.

Given the high mortality rate of patients with sarcoidosis-associated PH, evaluation for lung transplantation, when otherwise appropriate, should be considered early. Interestingly, angioplasty and stenting of the pulmonary artery with sustained haemodynamic and functional improvement has been reported in two sarcoid patients with extrinsic compression from mediastinal fibrosis [33].

## Conclusions

PH is a challenging complication of sarcoidosis in terms of both diagnosis and management. There are recent shreds of evidence suggesting that sarcoidosis-associated PH may be more complex than simply being the result of parenchymal lung disease and hypoxaemia. Intrinsic vasculopathy may play an important role. The presence of PH signifies a grave prognosis in patients with sarcoidosis. PAH-targeted therapy is tempting in sarcoidosis-associated PH but the lack of conclusive data leaves many uncertainties in this area. Although difficult to conduct in such a rare condition, prospective, randomised controlled trials are warranted. At the very least, great effort should be put into setting up international registries to obtain data from patients with sarcoidosis-associated PH.

### *Statement of Interest*

M. Humbert has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergènes, TEVA and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. D. Valeyre is a member of the advisory board of IPF InterMune. He has participated as an investigator or a member of steering committee in trials on IPF (CAPACITY, BUILD3 and BIBF) and the CENTOCOR trial on sarcoidosis. His accommodation at and travel to medical meetings (ATS, ERS and CPLF) was funded by AstraZeneca, GSK, Boehringer, Nycomed and PneumoPharma.

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# Chapter 15

# Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis

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**SUMMARY: In the recent classification of pulmonary hypertension (PH), pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) were grouped as a single subcategory within pulmonary arterial hypertension (PAH) because of specific similarities in their diagnosis, prognosis and management. These diseases are characterised by predominant involvement of small pulmonary veins (PVOD) or capillaries (PCH), and cannot be distinguished from idiopathic PAH (IPAH) by their clinical or haemodynamic presentation. Only histopathological examination can confirm the diagnosis, but lung biopsies are high-risk procedures and are not recommended. A less invasive approach combining computed tomography (CT) of the chest, carbon monoxide diffusion and bronchoalveolar lavage (BAL) may be helpful to screen PVOD or PCH patients. These patients have a poor prognosis and were at risk of developing pulmonary oedema with specific PAH therapy. Thus, lung transplantation remains the treatment of choice for PVOD and PCH. In patients with the most severe disease, the cautious use of specific PAH therapy can be proposed as a bridging therapy while the patient awaits a lung transplant.**

**KEYWORDS: Pulmonary capillary haemangiomatosis, pulmonary oedema, pulmonary veno-occlusive disease**

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Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) are classified as distinct subgroups of PAH and account for approximately 5–10% of the histological forms of cases first considered to be idiopathic pulmonary arterial hypertension (IPAH) [1]. Even though the first description of PVOD was reported in 1934 [2] and the first case of PCH was reported more than 30 years ago [3], the pathophysiology of these diseases remains poorly understood [4, 5]. While the pulmonary vascular pathology of IPAH or

heritable PAH is characterised by major remodelling of small pre-capillary pulmonary arteries, PVOD and PCH mainly affect the post-capillary pulmonary vessels including the small pulmonary veins (PVOD) and capillaries (PCH) [6–8]. Despite this anatomical difference, PVOD and PCH have a very similar clinical presentation to PAH but with a more severe prognosis. Indeed, PVOD and PCH were characterised by the risk of developing severe pulmonary oedema with specific PAH therapy, justifying the importance of an early diagnosis to propose specific management. A definitive diagnosis of PVOD and PCH requires histological analysis of a lung sample [9, 10]; however surgical lung biopsy is a very high-risk procedure in patients with pulmonary hypertension (PH) and is not recommended in this setting. The recent improved characterisation of these diseases proposes a less invasive diagnostic approach [4, 5, 11–14].

## Classification and definition

PAH, PVOD and PCH were believed to represent three different forms of the same disease spectrum, with lesions in different components of the vascular tree, *i.e.* arteriolar, venous or capillary lesions, respectively [7]. Because of the differences in pathological assessment and more severe prognosis, PVOD and/or PCH are now clearly identified as a specific subgroup of PAH in the classification of PH. Additionally, occlusive venopathy and capillary proliferation may occur in PAH associated with different conditions, as recently demonstrated to be frequently the case in PAH associated with connective tissue diseases (CTDs) [15, 16]. Pulmonary venopathy has also been reported in virtually all conditions associated with PAH.

## Pathological assessment

PVOD is characterised by post-capillary lesions involving septal veins and pre-septal venules, with muscularisation of the tunica media and loose, fibrous remodelling of the intima, which may lead to total occlusion of the lumen (fig. 1a). Fibrous occlusion of large septal veins is observed in many forms of secondary pulmonary venous hypertension; thus involvement of pre-septal venules should be considered as necessary for the diagnosis of PVOD. Pleural and pulmonary lymphatic vessels are usually dilated and signs of occult alveolar haemorrhage may be present [17]. Even if vascular lesions predominate within the septal and pre-septal veins, lesions frequently affect capillaries and small pulmonary arteries [6, 8]. In PVOD, pulmonary arterial lesions mainly consist of intimal thickening and medial hypertrophy; however, plexiform lesions are absent. Capillary changes are frequently observed, which include dilated congested capillaries and focal capillary angioproliferations, and it has been proposed that such proliferations may follow a chronic post-capillary obstruction [6, 7]. Thrombotic occlusion of small post-capillary microvessels may be present, corresponding to ''colander-like'' lesions.

In PCH, the abnormal proliferating capillaries extend into bronchovascular bundles and infiltrate the walls of arterioles, arteries, venules and veins (fig. 1b) [6]. LANTUEJOUL *et al.* [7] reviewed histological specimens from 35 patients who were originally classified with PVOD and PCH. In this series, PCH-like lesions were found in 24 (80%) out of 30 PVOD patients; conversely four (80%) out of five PCH patients showed significant venous involvement. Thus, these results have raised questions concerning a possible overlap between PVOD and PCH [7]. This hypothesis is reinforced by similar clinical and radiological presentations of PVOD and PCH [5, 12, 18, 19]. DORFMULLER *et al.* [15] recently reported the frequent involvement of pulmonary veins and capillaries in a PVOD-like pattern in PAH associated with CTDs.

In conclusion, these most recent insights into the pathology of PVOD and PCH may indicate a new approach to the disease with a less rigid perception of pre-capillary, post-capillary and capillary lesions in patients with PH.

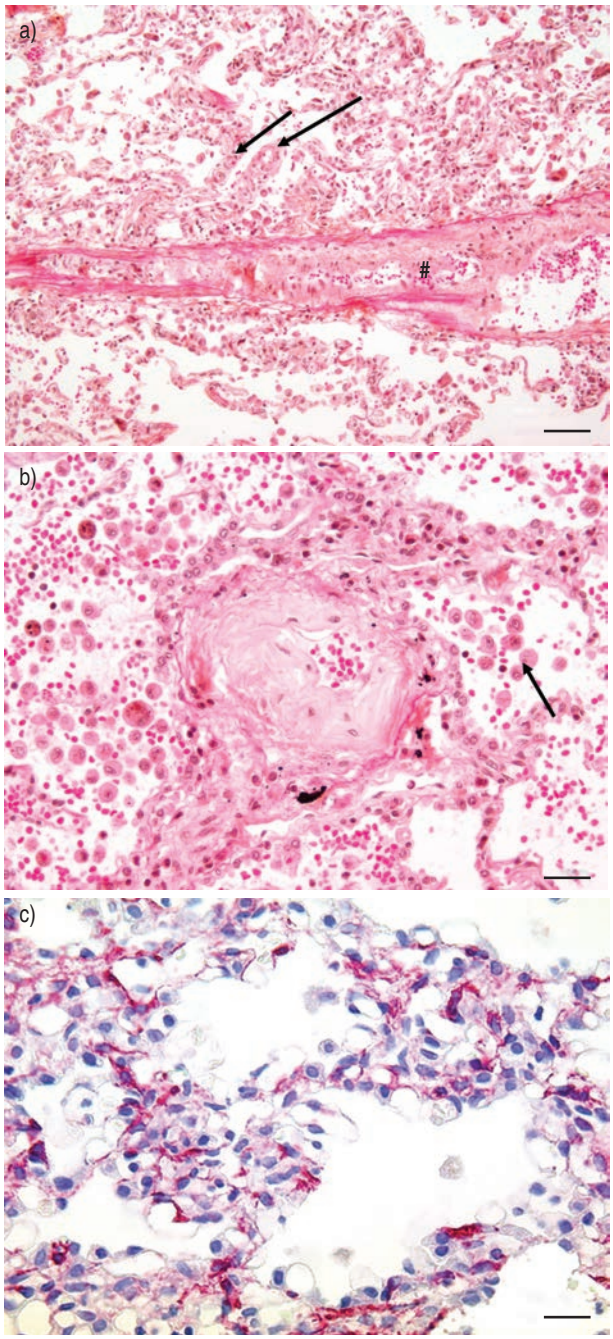


**Figure 1.** Pulmonary veins with obstructive venopathy in lungs of patients with pulmonary veno-occlusive disease and a case of pulmonary capillary haemangiomatosis. a) Fibrous obstruction of a septal vein (#) and pre-septal venules (arrows) (haematoxylin–eosin–saffron staining). b) Pre-septal venule with occlusive remodelling, note the intra-alveolar haemorrhage and siderin-laden macrophages (arrow) (haematoxylin–eosin–saffron staining). c) Excessive proliferate alveolar capillaries in a patient with pulmonary capillary haemangiomatosis, note protrusion of ectatic lumina into the alveoli (anti-CD31 staining). a) Scale bar=100 μm; b) scale bar=50 μm; c) scale bar=25 μm. Reproduced and modified from [5] with permission from the publisher.

# Pulmonary veno-occlusive disease

## Epidemiology

PVOD diagnosis has been reported in a very wide age range of patients, from those in their first weeks of life through to those in their more advanced years [3, 9, 10]. In contrast with IPAH, PVOD is not associated with a female predominance [3, 9]. The incidence of PVOD is clearly underestimated as many of these cases had been classified as IPAH. Usually, PVOD is considered to account for 5–10% of the histological forms of cases initially thought to be "idiopathic" [5, 10]. However, PVOD can also occur in patients with associated diseases including CTDs and, particularly, systemic sclerosis [15, 16, 20], sarcoidosis [21], pulmonary Langerhans' cell histiocytosis [10, 22, 23], HIV infection [24–26], bone marrow transplantation [27–33] and idiopathic pulmonary fibrosis (IPF) [34–36]. The association between these different conditions and PVOD suggests that prevalence of PVOD could be much higher. In national registries, PAH associated with connective diseases represents 15–30% of PAH patients [37, 38] but the true prevalence of pulmonary venopathy in PAH associated with CTDs is difficult to estimate as no studies include systematic assessments of venous involvement in these patients. However, small series reported a high prevalence of venous involvement in these settings. JOHNSON *et al.* [16] described a series of probable PVOD in four patients with scleroderma-associated PAH. DORFMÜLLER *et al.* [15] analysed lung samples from eight patients with end-stage PAH associated with CTDs and demonstrated that significant pulmonary vascular lesions predominating in veins or pre-septal venules were more frequently observed in PAH associated with connective tissue disease (75%) when compared with IPAH (17.2%).

## Risk factors

A definite association between PAH and appetite suppressants (aminorex,

fenfluramine and derivatives, and benfluorex) has been clearly demonstrated based on multicentre epidemiological studies [39–41]. In contrast with PAH, the association of risk factors with PVOD was rarely reported [3]. Chemical exposures have been suggested to play a role in the development of the disease and PVOD has been associated with various chemotherapy regimens including bleomycin, bis-chloroethylnitrosourea (BCNU) and mitomycin [42–45] and after bone marrow transplantation [27–33, 46].

We recently reported a higher tobacco exposure and an increased proportion of smokers in PVOD when compared with PAH [4]. Nevertheless, the reason why tobacco exposure would be a specific risk factor for PVOD remains unknown. This relationship is also supported by the described association between PVOD and pulmonary Langerhans' cell histiocytosis, a pulmonary disease occurring almost exclusively in smokers [22, 23, 47, 48].

## Hereditable PVOD

Genetic risk in the development of PVOD has been previously suggested by reports of occurrence in siblings [49, 50] and several bone morphogenetic receptor type II gene (*BMPR2*) mutations were reported [3, 51–53]. These reports demonstrate a probable role of the *BMPR2* pathway in the development of PVOD and support systematic screening for a familial history of pulmonary vascular disease and genetic counselling in PVOD patients. Indeed, in our experience of genetic counselling, the proportion of *BMPR2* mutations found in familial PVOD is lower than the proportion observed in the families of PAH patients (23% *versus* 84%, respectively).

## Clinical features

PVOD and IPAH share the same clinical presentation and clinical examination is not very helpful in distinguishing them. As observed in other forms of PAH, affected individuals most frequently report dyspnoea, exercise limitation, fatigue and syncope [1, 4, 9]. Haemoptysis may also occur but is rarely of significance. Progressive development of symptoms is typical, though the acute manifestation of PVOD or even presenting with sudden death has been described. Auscultation is usually normal, but auscultatory crackles may occur in the context of pulmonary oedema [9]. Physical examination is characterised by typical signs of PH. Digital clubbing and Raynaud's phenomenon have been reported in PVOD but recent series suggested that Raynaud's phenomenon (8% of PVOD patients) and digital clubbing (16%) remain rare in PVOD and can also be found in the same proportion in IPAH [4].

## Haemodynamic characteristics

All patients suspected of having PAH, PVOD or PCH on the basis of clinical assessment and non-invasive testing should undergo right heart catheterisation (RHC) in order to confirm the diagnosis and establish the extent of haemodynamic perturbation [1]. In a large series comparing patients with biopsy-proven IPAH and PVOD, we found that PVOD and PAH shared broadly similar haemodynamic characteristics, and we confirmed that PVOD patients were characterised by severe pre-capillary PH on RHC [4, 5]. Even if PVOD is histologically characterised by post-capillary obstruction (involvement of small pulmonary veins), pulmonary capillary wedge pressure ($P_{pcw}$) is normal in PVOD patients (*i.e.* $<$15 mmHg) [4, 5, 9, 11]. This is because the term $P_{pcw}$ is somewhat misleading as pressure measurements recorded when a catheter is wedged in a branch of the pulmonary artery reflects pressures in the larger veins that extend distally toward the heart, which are typically unaffected by the disease process (fig. 2) [3, 6]. Therefore, in PVOD the apparently normal values of $P_{pcw}$ do not represent a true reflection of the true capillary pressure. As a result, PVOD is characterised by a pattern of pre-capillary PAH on RHC even though the anatomic obstruction is predominantly post-capillary.

An acute vasodilator response has been reported in some PVOD cases [3, 54]. In a recent series, one patient with PVOD responded to nitric oxide; however, within 24 hours of initiation of

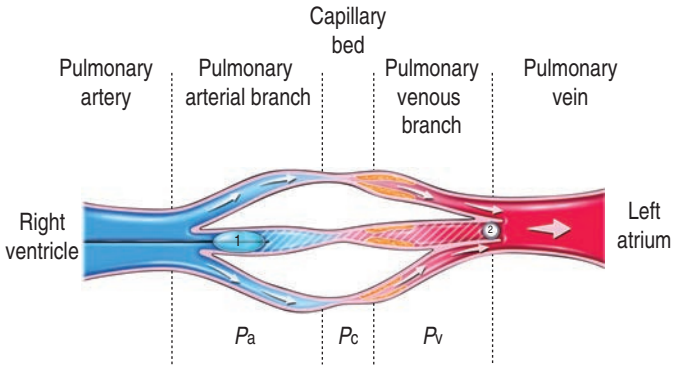


**Figure 2.** Diagram explaining why pulmonary capillary wedge pressure ($P_{pcw}$) is usually normal in pulmonary veno-occlusive disease (PVOD). PVOD mostly affects small pulmonary veins, leading to an elevation of pressure in this region ($P_v$) as well as to an elevation in true pulmonary capillary pressure ($P_c$) and pre-capillary pulmonary artery pressure ($P_a$). Larger pulmonary veins are usually not affected by PVOD, and it is in fact the pressure here that is reflected by $P_{pcw}$: the static column of blood (hatched) occluded by pulmonary arterial catheter wedging or balloon inflation of a pulmonary arterial branch (balloon 1) reflects the pressure in a vein of similar diameter (balloon 2), usually of a larger size than those vessels affected by PVOD. Therefore, this measurement technique does not reflect the important elevation of pressure in the smaller diameter vessels associated with PVOD. Reproduced from [5] with permission from the publisher.

calcium channel blocker (CCB) therapy, severe pulmonary oedema developed. An acute vasodilator response in PVOD was not predictive of a long-term response to CCBs, and should not be used when considered in the context of a positive acute test. However, acute testing with 10 ppm nitric oxide for a short period (5–10 minutes) is thought to be safe in patients with suspected PVOD but is unable to predict those patients in whom the initiation of PAH-specific therapy was associated with pulmonary oedema [4]. Given these observations, there may be little merit for performing vasodilator studies in patients with a strong clinical suspicion of PVOD, since the haemodynamic findings are unlikely to impact on therapeutic decisions.

## Non-invasive tools

In PVOD, histological proof is usually lacking as a surgical lung biopsy is a high-risk procedure that should not be performed. We have recently proposed a non-invasive approach involving arterial blood gases, pulmonary function tests, bronchoalveolar lavage (BAL) and high-resolution computed tomography (HRCT) of the chest to screen for patients with high probability of PVOD [4, 5].

### *Lung function testing and oxygenation parameters*

With the exception of occlusive venopathy associated with respiratory diseases, PVOD patients had generally normal pulmonary function tests analysed during spirometry and plethysmography [4]. However, measurements of the single-breath diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) are usually significantly reduced in PVOD, and to a greater degree than is the case in IPAH patients [4, 5]. In a previous series of biopsy-proven PVOD patients, we have shown that a $D_{L,CO}$ of $<$55% predicted may be useful to screen for PVOD cases among patients with suspected IPAH [4]. However, it is important to note that values for $D_{L,CO}$ may be overestimated in the context of PVOD, because of the frequent association with occult alveolar haemorrhage and values in the normal range do not exclude the diagnosis. In PVOD patients, baseline arterial oxygen tension ($P_{a,O_2}$) at rest is significantly lower than IPAH ($61 \pm 17$ and $75 \pm 14$ mmHg, respectively) [4]. Furthermore, even though PVOD patients have similar 6-minute walking distance (6MWD) at baseline when compared with IPAH, MONTANI *et al.* [4] showed that PVOD patients had a significantly lower nadir of arterial oxygen saturation measured by pulse oximetry ($S_{p,O_2}$) during the 6-minute walk test (6MWT) ($80 \pm 9$ and $87 \pm 7$%, respectively) [4].

### *Bronchoalveolar lavage*

Bronchoscopy is not a routine investigation in PAH but there may be a role for BAL in patients with suspected PVOD [11]. It has been described previously that bronchoscopic airway inspection may show hyperaemia of the lobar and segmental bronchi due to vascular engorgement [55]. Compared with PAH, RABILLER *et al.* [11] found a significantly elevated percentage of haemosiderin-laden macrophages and a higher Golde score [56], in keeping with the hypothesis of an occult alveolar haemorrhage in PVOD.

### *Imaging studies*

Chest radiographs and HRCT of the chest may show Kerley B lines or pleural effusions when pulmonary oedema occurs after initiation of specific PAH therapy [4, 9, 18, 57, 58]. With the exception of this situation, HRCT showed a significantly higher frequency of centrilobular ground-glass opacities, septal lines and mediastinal lymph node enlargement in PVOD compared with IPAH (fig. 3) [4, 9, 12, 18]. MONTANI *et al.* [4] demonstrated that the presence of two or three of these radiological abnormalities were observed in 75% of PVOD patients, but could also be present in IPAH (15%) patients. In contrast, the absence of radiological abnormalities on HRCT does not rule out PVOD [4].

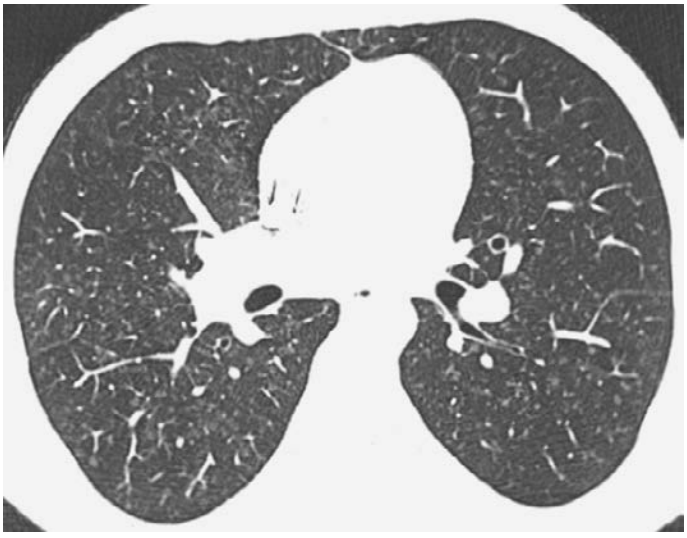

**Figure 3.** High-resolution computed tomography (HRCT) of the chest in a patient with pulmonary veno-occlusive disease. The HRCT displays marked ground-glass opacities with centrilobular pattern, poorly defined nodular opacities and septal lines.

In conjoint European Respiratory Society (ERS) and European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PH [1], it has been suggested that unmatched perfusion defects suggest the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) but also PVOD. However, this statement is based on few isolated reports of PVOD patients with "high probability ventilation/perfusion ratio ($V'/Q'$) lung scan", mimicking proximal CTEPH [59]. In a recent study, SEFERIAN *et al.* [60] reviewed $V'/Q'$ lung scans of 70 IPAH or heritable PAH and 56 PVOD patients. The authors demonstrated mismatched perfusion defects on $V'/Q'$ lung scans are an uncommon observation in IPAH or heritable PAH and PVOD patients and $V'/Q'$ lung scanning may mimic CTEPH in the same proportion in both conditions [60].

These findings suggest that non-invasive testing could be helpful to suggest the diagnosis of PVOD in patients with pre-capillary PH. A low resting $P_{a,O_2}$, low $S_{p,O_2}$ during 6MWD, low $D_{L,CO}$, presence of an occult alveolar haemorrhage and radiological abnormalities on a HRCT scan of the chest may identify a subgroup of patients with a high probability of PVOD and, therefore, avoidance of hazardous and invasive surgical procedures in these patients.

## Management

Even if baseline haemodynamics, New York Heart Association (NYHA) functional class and 6MWD are similar to those observed in PAH patients, PVOD patients have a worse outcome. Data suggests that the 1-year mortality rate may be as high as 72% [9], and the most recent series of 24 histologically confirmed severe PVOD patients found a mean $\pm$ SD time from diagnosis to death or lung transplantation of $11.8 \pm 16.4$ months compared to $42.3 \pm 29.9$ months in IPAH [4]. Interestingly, patients displaying PAH associated with CTDs have a more severe outcome than IPAH patients, and it can be suggested that this poor prognosis may be due at least, in part, to the frequent pulmonary venous involvement in these conditions [15, 16]. Excluding lung transplantation, treatment options are unfortunately limited in PVOD, highlighting the importance of introducing a non-invasive approach to screen for PVOD and consideration of lung transplantation earlier in the course of the disease.

### *Conventional therapy*

Severe resting hypoxaemia and exertional desaturation are frequently observed in PVOD patients justifying oxygen therapy to maintain saturation above 90% [1]. Conventional therapy includes high-dose diuretics in order to decrease the risk of pulmonary oedema. Even if there are no specific data in PVOD, the rationale for anticoagulation is present because of the subsequent *in situ* thrombosis [6].

No evidence supports the possible role of immunosuppressive therapy in PVOD, except in the context of venous involvement associated with connective tissue disease [61]. In this context, PAH patients with mixed CTD and systemic lupus erythematosus (SLE) (but not scleroderma) may improve with immunosuppressive therapy [62, 63].

The additional haemodynamic stresses of pregnancy and delivery are poorly tolerated in PAH or PVOD patients, as they are associated with an increased rate of deterioration and very high mortality rates. Therefore, female patients with child-bearing potential should be counselled on effective contraception measures.

### *Specific PAH therapy*

The major concern with specific PAH therapy in PVOD is the risk of severe pulmonary oedema, which has been reported with all specific PAH therapies (prostacyclin and its derivatives, endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE-5 I) and CCBs) [3, 64, 65]. The mechanism, it is understood, is due to the relative vasodilatation of the pre-capillary vessels, which exceeds that of the pulmonary capillaries and veins, and is associated with an increase in pulmonary blood flow, an increase in transcapillary hydrostatic pressure and transudation of fluid into the pulmonary interstitium and alveoli [5].

In our cohort of histologically confirmed PVOD patients, seven out of 16 patients who received specific PAH therapy, developed pulmonary oedema and none of the clinical, functional or haemodynamic characteristics were predictive of the occurrence of pulmonary oedema [4]. Nevertheless, clinical improvement or stabilisation has been reported with continuous intravenous epoprostenol, iloprost (Bayer Schering Pharma, Berlin-Wedding, Germany) and sildenafil [9, 66–73]. While pulmonary vasodilators have an established efficacy in the treatment of PAH [74, 75], the benefit of these treatments for patients with PVOD remains unclear. Continuous *i.v.* epoprostenol therapy has been shown to improve haemodynamics in some cases of PVOD [9, 68, 71, 72].

We have recently shown how, in carefully selected individuals, that epoprostenol may have a therapeutic role as a bridge therapy to lung transplantation [76]. In this study, 12 patients with advanced PVOD were treated with continuous *i.v.* epoprostenol at the French National Referral Centre (Le Kremlin-Bicêtre, France). Because of the possibility of severe adverse reactions, relatively slow increments in dose titration (median dose of 13 $ng \cdot kg^{-1}$ per minute) were made and high-dose diuretics were used. After 3–4 months of therapy, significant improvements in the NYHA functional class and haemodynamic indices were observed. Epoprostenol was generally well tolerated, with mild pulmonary oedema developing in only one patient. Lung transplantation, which was proposed for all patients (median 2.4 months from initiation of epoprostenol), was successfully performed in 10 cases [77]. These results suggest that cautious use of *i.v.* epoprostenol might be helpful in the management of these patients as a bridge to lung transplantation. However, lasting improvements in clinical and haemodynamic indices are uncommon, and treatment with epoprostenol should be considered as a bridging therapy and not an alternative to transplantation.

### *Lung transplantation*

Lung transplantation remains the treatment of choice for PVOD and offers the possibility of cure for the disease [75, 77, 78]. Because of the more severe prognosis for PVOD patients, it may be necessary to discuss lung transplantation early on in the course of PVOD. At our centre, eligible PVOD patients with severe functional lung transplantation (class NYHA functional class III or IV) are, therefore, listed for lung transplantation at the time of diagnosis [5].

## Pulmonary capillary haemangiomatosis

PCH is defined by its pathological assessment showing localised capillary proliferation with possible infiltration of vascular, bronchial and interstitial pulmonary structures. PCH is usually associated with PH. However, in an autopsy series, the presence of isolated PCH-like foci findings have been reported in eight (5%) out of 140 patients without symptoms of PAH, suggesting that these isolated PCH-like foci may be incidental findings [79].

Interestingly, LANTUEJOUL *et al.* [7] reported that capillary proliferation was frequently observed in PVOD (73% of cases) and that significant venous involvement is present in 80% of cases initially diagnosed as PCH. The authors suggested that the majority of cases of PCH are a secondary angioproliferative process in response to a post-capillary obstruction associated with PVOD [7]. They proposed to use the term ''secondary PCH'' for PCH-like changes associated with different disorders, including PVOD, and to reserve the term of ''primary PCH'' for the rare case of isolated PCH without an identified cause [7]. Indeed, PCH and PVOD share the same clinical and radiological characteristics, and PCH can also be complicated by occult alveolar haemorrhage and severe pulmonary oedema with specific therapy. These findings raise the hypothesis that PCH and PVOD may be two aspects of the same disease, justifying their classification within the same subgroup for the classification of PH. An updated classification of PH was defined at the 4th World Conference on Pulmonary Hypertension in 2008 (Dana Point, CA, USA) [80]. The updated classification table can be found in chapter 2 along with further information on PH definitions and differentiations [81].

Very few data are available regarding patients with histologically confirmed PCH. ALMAGRO *et al.* [14] reported two cases of PCH and reviewed the characteristics of 35 PCH patients from the literature. Similar to PVOD, PCH was found to occur in patients aged from 2 to 71 years (mean age 29 years) with no female predominance observed (55% of PCH patients were male). Even if PCH appears to be sporadic in most of the cases, rare familial PCH was described [82].

As observed in IPAH or PVOD, dyspnoea and signs of right heart failure were the most frequent clinical signs observed. Based on small series, it seems that haemoptysis and pleural effusions were more frequently observed in PCH than in PVOD [14]. Indeed, ALMAGRO *et. al.* [14] reported that pleural effusion may be haemorrhagic in PCH (four of the nine PCH patients) [14]. Prognosis in PCH seems to be broadly similar to that described in PVOD and worse than in IPAH [4, 37].

In their literature review, ALMAGRO *et al.* [14] confirmed that the $P_{pcw}$ is usually normal in PCH (14 out of 16 patients in this series). Several reports found that in PCH the same radiological abnormalities are present on HRCT scans of the chest that are described in PVOD. These abnormalities were non-specific and include septal lines, centrolobular ground-glass opacities, lymph node enlargement and pleural effusion [14, 18, 72]. Very few data are available on pulmonary function tests in PCH. ALMAGRO *et al.* [14] reported diminished $D_{L,CO}$ and hypoxaemia in PCH patients but these finding may also be found in PVOD and to a lesser extent in IPAH [14, 83].

Regarding specific therapy, only a few PCH patients have been reported to be treated in the literature. In the vast majority of cases, prostacyclin had to be withdrawn because hemodynamic intolerance or pulmonary oedema [14, 84]. Even if prostacyclin was used without specific cautions in these reported cases, its use seems to be associated with a very high frequency of clinical deterioration and pulmonary oedema. No data exist regarding recent oral specific PAH therapies (PDE-5 I and ERAs). Corticosteroids have been initiated in some PCH patients without any effect on disease evolution [14]. Clinical improvements have been reported in PCH with interferon α-2a [85, 86]. However, these results involve few patient numbers and have never been confirmed in larger series. Because of the more severe prognosis of PCH, the treatment of choice for PCH remains urgent lung transplantation. To the best of our knowledge, no case of PCH recurrence was reported in the transplanted lungs.

## Conclusion

In conclusion, PVOD and PCH share similar clinical, functional and radiological characteristics and can be associated with occult alveolar haemorrhage. Clinical examination and haemodynamics are not helpful to discriminate PVOD, PCH and IPAH. A stepwise non-invasive approach including pulmonary function tests (low $D_{L,CO}$, hypoxaemia at rest, low $S_{p,O_2}$ during 6MWD), CT scans of the chest (septal lines, centrilobular ground-glass opacities and lymph node enlargement) and BAL, may be helpful in screening patients displaying PVOD/PCH. Indeed, PVOD and PCH are characterised by a very poor prognosis and the possibility of severe pulmonary oedema after initiation of specific PAH therapies. Even if some specific PAH therapies may be useful in PVOD, transplantation remains the treatment of choice for these two devastating diseases.

### *Statement of Interest*

D. Montani has relationships with drug companies including Actelion, Bayer, GSK, Lilly, Pfizer and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, fees for speaking and membership of scientific advisory boards. L. Price has received an educational grant from Pfizer, a fee for speaking from Actelion and travel to the ERS congress in 2011 was funded by GSK. O. Sitbon has relationships with pharmaceutical companies including Actelion, Bayer HealthCare, GSK, Lilly, Pfizer and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, membership of scientific advisory boards, fees for speaking, funds for research and reimbursement for attending symposia. M. Humbert has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergènes, TEVA and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

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# Chapter 16

# Obesity and pulmonary hypertension

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**SUMMARY: Obesity is an increasingly recognised global health problem. Obesity, insulin resistance and hyperlipidaemia are commonly referred to as the metabolic syndrome, which has long been implicated in the pathogenesis of systemic vascular disorders. The link between obesity and pulmonary vascular diseases, however, is a more recent debate that includes three aspects: 1) obesity as an active contributor in the pathogenesis of pulmonary arterial hypertension (PAH) of World Health Organization (WHO) group 1; 2) the association of pulmonary vasculopathy with obesity, in the setting of obesity cardiomyopathy (this entity belongs to the pulmonary hypertension (PH) of WHO group 2); and 3) PH in the setting of obesity hypoventilation syndrome (OHS), which is part of WHO group 3. In this chapter, we will review the current understanding in pathophysiology and clinical manifestations of these three pulmonary vascular disorders.**

**KEYWORDS: Heart failure with preserved ejection fraction, metabolic syndrome, obesity, obesity cardiomyopathy, obesity hypoventilation syndrome, pulmonary arterial hypertension**

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Obesity is defined as a body mass index (BMI) of $\geqslant 30$ kg·m$^{-2}$ [1]. Obesity is one of the leading health issues worldwide, resulting in about 300,000 deaths per year in the USA [2]. In 1997, the World Health Organization (WHO) formally recognised obesity as a global epidemic [3]. As of 2008, WHO claimed that 1.5 billion adults were overweight (BMI $\geqslant 25$ kg·m$^{-2}$) and of these, over 200 million males and nearly 300 million females were obese [4].

Once considered a problem only of high-income countries, obesity rates are rising worldwide. These increases have occurred most dramatically in urban settings. In the European Union, the proportion of obese people in the adult population varied in 2008–2009 between 8 and 23.9% for females and between 7.6% and 24.7% for males [5]. The USA has the highest obesity rates in the developed world [6]. From 1980 to 2002, obesity rates have doubled, reaching the current rate of 33% of the adult population [7]. In addition, another third of Americans are overweight, defined as a BMI $<30$ but $>24$ kg·m$^{-2}$. Presently, about 65% of Americans are now considered either overweight or obese [8]. While the overall rate of obesity started to plateau in the last decade, severe obesity and obesity in children continues to rise [9].

Idiopathic pulmonary arterial hypertension (IPAH) is considered a rare disease, with an incidence of less than one case per 100,000 people. These patients are also affected by obesity and there are

emerging data suggesting that obesity itself or its related comorbidities may participate in the development and/or progression of pulmonary arterial hypertension (PAH) [10, 11]. Pulmonary hypertension (PH) due to left heart disease (LHD) is a readily recognised complication of obesity. Heart failure with preserved ejection fraction (HFPEF), sometimes referred to as heart failure due to left ventricular (LV) diastolic dysfunction, accounts for nearly one-half of all hospitalisations for heart failure in the USA [12] and is becoming an increasingly common aetiology for PH of WHO group 2 [13]. Part of this increase is probably due to the rising prevalence and severity of obesity, which has a strong association with heart failure. In addition, it is well recognised that obesity leads to major abnormalities of metabolism that adversely affect vascular function. These abnormalities, which include insulin resistance and hyperlipidaemia, are commonly referred to as the metabolic syndrome and have long been implicated in the pathogenesis of systemic vascular disease. More recently, a growing body of literature suggests that the metabolic syndrome may also contribute to the pathogenesis of pulmonary vascular disease and, in particular, PAH [14, 15].

In this chapter, we will discuss three major aspects of PH in the setting of obesity: 1) the relationship between obesity and PAH (WHO Group 1), and possible mechanistic implications of obesity in the development and/or worsening of PAH; 2) the link between obesity and PH due to left heart failure (within this category, we will touch upon aspects of passive pulmonary vascular congestion and specific haemodynamic characteristics of PH in the setting of obesity, as well as the development of a reactive pulmonary vasculopathy associated with a disproportionate increase in transpulmonary gradient, and the emergence of an abnormal pulmonary vascular resistance (PVR)); and 3) we will review the occurrence of PH and cor pulmonale in the setting of obesity hypoventilation syndrome (OHS).

## Obesity and PAH (WHO group 1)

### Epidemiology

The prevalence of obesity in PAH seems to parallel that of the rest of the population. A single-centre study found no correlation between BMI and the diagnosis of PH when these patients were compared with US National Health and Nutrition Examination Survey (NHANES) controls [11]. Nevertheless, the distribution of obesity seems to vary according to aetiology. A recent evaluation of the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) determined that, while the mean BMI was no different in PAH patients compared with NHANES controls, significantly more PAH patients were obese (36.5% *versus* 33.0%, $p=0.004$) and underweight (5.7% *versus* 4.1%, $p=0.003$) [16]. IPAH and PAH associated with anorectic drugs and certain toxins had significantly more obese patients compared with the controls (40.1% *versus* 32.5% and 59.6% *versus* 35.0%, respectively; both $p<0.001$). In this registry, obese IPAH patients were significantly older, more often black, more often functionally impaired, had more comorbidities and were on more PAH therapies, although with similar mean pulmonary artery pressures ($P_{pa}$) and pulmonary vascular resistance (PVR) indices (table 1). It is noteworthy that the REVEAL database includes patients with baseline pulmonary capillary wedge pressures ($P_{pcw}$) of up to 18 mmHg, and therefore may include aetiologies other than PAH (WHO group 1). Nevertheless, there were similar proportions of patients with traditional $P_{pcw}$ values of 15 mmHg or less in the obese and non-obese subgroups. As sleep apnoea has been shown to correlate with obesity, obese patients with IPAH were more likely to have a history of sleep apnoea than non-obese patients with IPAH, which in turn may contribute to the severity of PAH. In contrast, patients with PAH associated with congenital diseases and connective tissue disease (CTD) were more often underweight than their healthy controls.

Metabolic syndrome, including glucose intolerance due to insulin resistance, systemic hypertension and dyslipidaemia, has become increasingly prevalent in obese patients. Metabolic syndrome and insulin resistance are associated with systemic cardiovascular disease, idiopathic cardiomyopathy [17] and congestive heart failure [18]. Recent data suggest that there is also a link

**Table 1.** Characteristics of obese and non-obese patients with idiopathic pulmonary arterial hypertension (IPAH) enrolled in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) at the time of pulmonary arterial hypertension (PAH) diagnosis

| | Obese[#] | Non-obese[¶] | p-value[+] |
|---|---|---|---|
| **IPAH patients n** | 369 | 552 | |
| **Age at PAH diagnosis years** | 49.7±13.7 | 45.2±19.3 | <0.001 |
| **Race** | | | |
| White | 288 (79.1) | 401 (73.4) | 0.02 |
| Black | 46 (12.6) | 64 (11.7) | |
| Hispanic | 24 (6.6) | 46 (8.4) | |
| Asian/Pacific Islander | 4 (1.1) | 22 (4.0) | |
| Native American/Native Alaskan | 1 (0.3) | 2 (0.4) | |
| Other | 1 (0.3) | 11 (2.0) | |
| **WHO/NYHA FC at PAH diagnosis** | | | |
| I | 7 (2.4) | 22 (5.2) | 0.009 |
| II | 48 (16.7) | 105 (25.0) | |
| III | 184 (64.1) | 233 (55.5) | |
| IV | 48 (16.7) | 60 (14.3) | |
| **Haemodynamics at diagnosis** | | | |
| Mean $P_{ra}$ mmHg | 11.8±6.1[f] | 9.2±5.3[¶¶] | <0.001 |
| Mean $P_{pa}$ mmHg | 54.0±13.3[##] | 53.3±14.1 | NS |
| Cardiac output L·min$^{-1}$ | 4.5±1.4 | 3.9±1.4 | <0.001 |
| CI L·min$^{-1}$·m$^{-2}$ | 2.2±0.7 | 2.4±1.0 | <0.001 |
| PVR Wood unit | 11.3±6.0 | 13.5±8.3[++] | <0.001 |
| PVRI Wood unit·m$^2$ | 23.7±12.3 | 22.5±13.2[++] | NS |
| **Comorbidities at enrolment[§]** | | | |
| Sleep apnoea | 146 (42) | 81 (15.5) | <0.001 |
| Diabetes mellitus | 81 (22.9) | 37 (6.8) | <0.001 |
| Hypertension | 176 (49.7) | 161 (29.7) | <0.001 |
| Renal insufficiency | 20 (5.7) | 20 (3.7) | NS |
| **Use of statins[§]** | 77 (21.8) | 58 (10.7) | <0.001 |
| **Use of diuretics[§]** | 267 (75.4) | 338 (62.4) | <0.001 |

Data are presented as mean±SD or n (%), unless otherwise stated. WHO: World Health Organization; NYHA: New York Heart Association; FC: functional class; $P_{ra}$: right atrial pressure; $P_{pa}$: pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; NS: nonsignificant. [#]: body mass index (BMI) ⩾30 kg·m$^{-2}$; [¶]: BMI <30 kg·m$^{-2}$; [+]: Chi-squared test for categorical data and t-test for continuous data; [§]: data not available at time of PAH diagnosis; [f]: n=339; [##]: n=269; [¶¶]: n=501; [++]: n=551. Reproduced and modified from [16] with permission from the publisher.

between insulin resistance and PAH. In a single-centre study that compared 81 nondiabetic females with PAH to 967 females without PAH from the NHANES study, females with PAH were more likely to have insulin resistance (45.7% *versus* 21.5%) and less likely to be insulin sensitive (43.2% *versus* 57.8%) [11]. This study used fasting triglyceride (TG) to high-density lipoprotein cholesterol ratio as a surrogate of insulin sensitivity, and showed that the presence of insulin resistance and a higher New York Heart Association (NYHA) functional class were associated with poorer 6-month event-free survival (58% *versus* 79%). An additional study of 41 PAH patients found that 56% had insulin resistance, defined as a haemoglobin A1c level of ⩾6.0%, and 15% had unrecognised diabetes mellitus, supporting the high prevalence of insulin resistance in PAH [19].

## Pathophysiology of PAH: is there a direct link between obesity and PAH?

Inflammatory processes involving cytokines, chemokines and growth factors have been increasingly recognised to play an important role in the vascular remodelling characteristics of different forms of PAH, such as IPAH, PAH associated with CTD, and HIV infection [20]. Insulin resistance is also associated with an abnormal milieu of elevated inflammatory cytokines [21]. Moreover, similar inflammatory molecules, such as interleukin (IL)-6 [22], monocyte chemotactic protein (MCP)-1 [23] and peroxisome proliferator-activated receptor (PPAR)-γ, have been

implicated in the pathogenesis of both PAH and insulin resistance [24]. At the same time, antioxidants such as apolipoprotein E (ApoE), which is a protective factor known to reduce oxidised low-density lipoprotein and atherogenesis, are suppressed in obesity, probably due to increased oxidative stress [25]. Genetically altered ApoE-deficient mice develop both insulin resistance and PAH when fed a high-fat diet. This PAH is characterised by pulmonary vascular remodelling and right ventricular (RV) hypertrophy, and is not due to LV dysfunction [24]. Further, the ApoE-knockout mice have decreased levels of adiponectin, which suppresses platelet-derived growth factor (PDGF)-induced proliferation of pulmonary vascular smooth muscle cells isolated from ApoE-knockout or wild-type mice. In addition, the PPAR-γ agonist rosiglitazone increases plasma adiponectin levels eight-fold in male ApoE-knockout mice, leading to improved insulin sensitivity and complete regression of pulmonary vascular disease. Although it is difficult to separate the effects of insulin resistance from those of ApoE and adiponectin, taken together, these results suggest that insulin resistance may be a risk factor for PAH and that deficiency of ApoE and/or adiponectin plays a role in this interaction. Further links between obesity and PAH implicating adiponectin have been suggested from studies showing that adiponectin is localised to the pulmonary vascular endothelium, and that adiponectin deficiency in knockout mice leads to an age-dependent increase in $P_{pa}$ and vascular remodelling, which is associated with inflammatory cells [26].

Obesity and the metabolic syndrome are also associated with decreased circulating levels of natriuretic peptides. Large cross-sectional studies have shown lower plasma levels of N-terminal (NT) atrial natriuretic peptide (ANP) and NT brain natriuretic peptide (BNP) in patients with insulin resistance, obesity and diabetes. In one study, plasma natriuretic peptide levels were inversely associated with all components of the metabolic syndrome except for elevated blood pressure [27]. In males and females with the metabolic syndrome, adjusted levels of ANP were 16% and 18% lower and levels of BNP were 24% and 29% lower, respectively, compared with those without it. In another study comparing those with and without the metabolic syndrome, RUBATTU *et al.* [28] found that plasma levels of NT-proANP are significantly reduced in hypertensive patients with the metabolic syndrome and inversely related to LV mass. Considering the prominent role that natriuretic peptides play in mitigating maladaptive cardiac hypertrophic responses [29, 30], this is one mechanism by which obesity and the metabolic syndrome may predispose to LV hypertrophy and diastolic dysfunction. In addition, reduced natriuretic peptide levels may contribute to pulmonary vascular pathology in the metabolic syndrome in multiple other ways, considering that they are not only natriuretics, but also pulmonary vasodilators, inhibitors of proliferation of pulmonary vascular smooth muscle cells and repressors of the secretion of pro-inflammatory cytokines, such as IL-6 and tumour necrosis factor (TNF)-α, in addition to several chemokines and adipokines, such as leptin and retinol-binding protein (RBP)-4 [31].

### Treatment of obesity in PAH: need for further clarification

The accumulating evidence summarised here suggesting that obesity may have an adverse effect on the pulmonary vasculature raises the question of whether weight loss has a mitigating effect. Although there have been occasional case reports describing a favourable pulmonary hypertensive response to bariatric surgery [32], there is still a lack of data on whether weight loss, a known therapeutic option for systemic vascular disease, has direct benefits on the pulmonary vasculature. Similarly, there is a lack of data on whether presently available PAH-specific therapies have a beneficial effect on obesity-related PH or on weight loss itself. Clearly, more research is needed in this area.

## Obesity and its relationship with PH (WHO group 2)

### The heart as a metabolic organ: mechanisms of lipotoxic cardiomyopathy

Obesity has long been recognised as an important risk factor for heart disease, due to its association with traditional risk factors for cardiovascular disease, such as systemic hypertension,

diabetes and dyslipidaemia. Historically, a direct effect of obesity on the heart was posited in the 19th century by LAENNEC [33] and VIRCHOW [34], who described intracellular deposition of fat in cardiomyocytes. Mounting evidence from research studies suggests that not only are TGs deposited in significant excess in cardiac myocytes of the obese, but also that dysregulated metabolism of fatty acids leads to cell damage and, ultimately, cell death [35]. This process probably contributes to decreased compliance of the LV and the development of LV diastolic dysfunction, which in turn generates passive elevation of pulmonary venous pressure and produces PH. Therefore, it may be just as important to evaluate the effects of obesity on the pulmonary vasculature as it is on the systemic circulation.

## Animal models of cardiac lipotoxicity

Deciphering the independent effect of lipid accumulation in cardiac myocytes on global cardiac function has been challenging. A commonly used model for fatty heart is the Zucker diabetic fatty (ZDF) rat, in which a loss of function mutation in the leptin receptor stimulates eating behaviour, obesity and ectopic lipid accumulation, including the development of lipotoxic cardiomyopathy (fig. 1) [35, 36]. In addition, two non-obese transgenic mouse models that are characterised by accumulation of fatty acids in cardiomyocytes have been developed, one which has cardiac-specific overexpression of the acyl-coenzyme A (acylCoA) synthase gene develops cardiac hypertrophy, LV dysfunction and premature death [37]. This model is characterised by accumulation of fatty acids in cardiomyocytes. These effects can be prevented by administration of leptin, which increases fatty acid oxidation and reduces the cardiac content of TG. Another model of fatty heart is produced *via* manipulation of PPAR-$\alpha$, an important regulator of multiple enzymes that oxidise fatty acid. Interestingly, both knocking out and overexpressing PPAR-$\alpha$ cause accumulation of lipid in the myocardium [38, 39], suggesting a complex interaction between fatty acid and the mitochondrial enzymatic system of the heart. In addition, targeting genes affecting lipid delivery [40], synthesis [37] or secretion [41] in rodent models leads to lipid accumulation in the heart with consequent cardiac dysfunction.

Taken together, these data support the concept that cardiac-specific steatosis independent of systemic obesity is a direct cause of cardiomyopathy in animal models. More importantly, treatment of early disease in rodents is successful in improving the cardiac abnormalities even independent of body weight [36], suggesting a potential pharmacological target for treating heart disease in obesity (table 2).

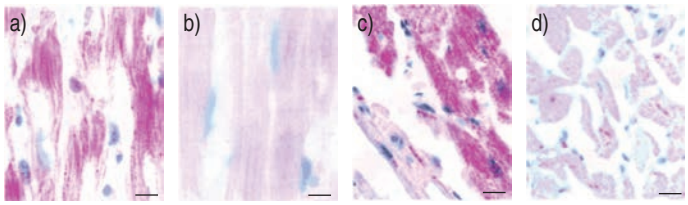


**Figure 1.** Cardiac lipodystrophy in animals and humans. Oil Red O staining for lipids in human and rat heart showing similarity of excess lipid deposition in obesity. Frozen sections. Cardiac muscle samples from a) an untreated obese Zucker diabetic fatty (ZDF) (*fa/fa*) rat or b) from a troglitazone-treated obese ZDF rat. Autopsy material of human cardiac muscle from c) a 57-year-old obese male (body mass index (BMI) 42 $kg \cdot m^{-2}$) or d) a 67-year-old lean male (BMI 28 $kg \cdot m^{-2}$). There is accumulation of Oil Red O-stained lipids in samples from both the obese human, presumably diet-induced, and the untreated ZDF rat with monogenic obesity. Scale bars=10 μm. Reproduced and modified from [35] with permission from the publisher.

## The obese heart in humans

Recent studies on the effect of obesity on cardiac function in humans have used noninvasive approaches [42]. In a study of 30 morbidly obese, asymptomatic patients evaluated for bariatric surgery, 43% had enlarged LVs and 54% had enlarged left atria [43]. Systolic dysfunction was found in 10% and diastolic dysfunction in 55% of subjects. 83% of patients had histories of systemic hypertension, of which 63% had their pressure under control using medication. Recently, magnetic resonance spectroscopy has

been used to quantify the lipid content in human cardiac muscle (fig. 2). Myocardial fat was found to be increased in obese compared to lean subjects and it correlated with free fatty acid levels, epicardial fat and waist to hip ratio [44]. Furthermore, this increased myocardial TG content appears to be mostly intracellular, as assessed by Oil Red O staining, and is associated with impaired filling of the LV (fig. 3) [42, 45]. In addition, epicardial fat was positively associated with peripheral vascular resistance and negatively with cardiac index. Therefore, cardiac accumulation of TG may be related to free fatty acid exposure, generalised ectopic fat deposition and peripheral vascular resistance, and these changes precede LV overload and hypertrophy [45, 46].

Although the TG content of the RV has yet to be examined, the haemodynamic finding of disproportionate right atrial hypertension seen in some patients suggests that the RV may have increased myocardial TG content as well.

## Pathophysiology and haemodynamics of obesity: effects on the pulmonary vasculature

The haemodynamic characteristics of obese patients include increased blood volume and stroke volume in proportion to the excess in body weight, with resultant increased cardiac work due to increased stroke work. In 10 obese volunteers who underwent left heart catheterisation and right heart catheterisation (RHC), DE DIVITIIS *et al.* [47] found that the majority of subjects had abnormally high RV and LV end-diastolic pressures, mean $P_{pcw}$, mean $P_{pa}$, PVRs, mean arterial pressures and systemic vascular resistances. In addition, both mean $P_{pcw}$, which had prominent "a" waves, and LV end-diastolic pressures correlated significantly with weight. LV stroke index and cardiac index were normal. In addition, the maximum oxygen uptake ($V'O_2$) was reduced, suggesting an intrinsic myocardial abnormality.

One of the few studies of RV function in morbidly obese patients was performed by ALPERT *et al.* [48], who noninvasively evaluated RV size and function at rest and with exercise in 22 obese subjects with no cardiopulmonary comorbidities. They found a significant negative correlation between per cent over ideal body weight and RV exercise response as defined by the change in RV ejection fraction during peak exercise ($r=0.86$, $p<0.00005$) and between RV internal dimensions and RV exercise response ($r=0.60$, $p<0.005$). The subgroup with a high-normal or enlarged RV internal dimension ($\geq 2.0$ cm, $n=10$) experienced no significant change in RV ejection fraction with exercise, whereas the subgroup whose RV internal dimension was less than 2.0 cm ($n=12$) experienced a significant increase in RV ejection fraction from $44\pm10\%$ at rest to $58\pm11\%$ at peak exercise ($p<0.03$), suggesting that in morbidly obese individuals without underlying cardiopulmonary disease, RV dilatation is probably accompanied by RV systolic dysfunction. Morbid obesity can also affect systolic function of the LV, although this has not been consistently reported [49, 50].

**Table 2.** Improvement in left ventricular (LV) function in obese Zucker diabetic fatty (ZDF) rats treated with troglitazone (TGZ)

| | Genotype | Body weight g | Heart weight g | RV weight g | LV weight g | LVEDD mm | LVESD mm | Fractional shortening % | Fractional area shortening % |
|---|---|---|---|---|---|---|---|---|---|
| **Lean wild type** | *+/+* | 394±6 | 1.20±0.01 | 0.20±0.01 | 0.85±0.01 | 7.3±0.3 | 4.2±0.4 | 43±6 | 65±8 |
| **Obese ZDF** | *fa/fa* | 572±24* | 1.55±0.17 | 0.25±0.02 | 1.06±0.01 | 7.8±0.7 | 5.0±0.8* | 36±7* | 56±9* |
| **TGZ-treated ZDF** | *fa/fa* | 611±7# | 1.78±0.29 | 0.24±0.02 | 1.04±0.02 | 7.6±0.5 | 4.0±0.6# | 48±7# | 69±7# |

Data are presented as mean±SEM. Rats given TGZ 200 mg·kg$^{-1}$ per day for 13 weeks had echocardiographic improvement in LV function, even in the absence of weight loss. RV: right ventricular; LVEDD: LV diastolic diameter; LVESD: LV systolic diameter. *: $p<0.05$, untreated ZDF *versus* wild-type rats; #: $p<0.05$, TGZ-treated ZDF *versus* untreated ZDF rats. Reproduced and modified from [36] with permission from the publisher.

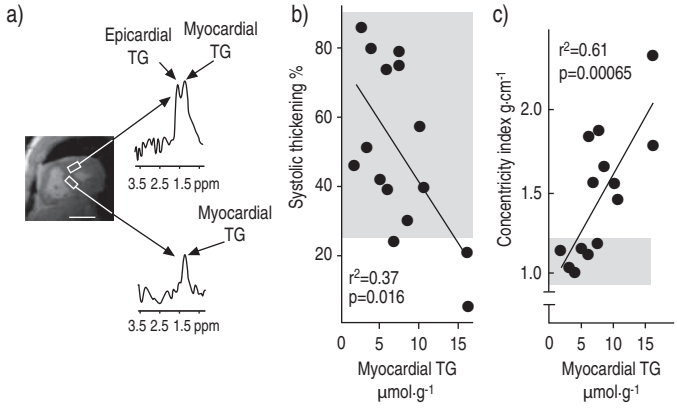


**Figure 2.** Myocardial triglycerides (TGs) and systolic function in humans. *In vivo* evaluation by localised proton spectroscopy and cardiac imaging. a) Selection of volume of interest in the ventricular septum and in the left ventricular (LV) wall with corresponding spectra. Spectrum from septum displays single resonance from myocardial TG. Spectrum from LV wall contains additional resonance from epicardial fat. Scale bar=2 cm. b) Myocardial TG is inversely correlated with the regional systolic function measured as septal thickening. Normal range of septal thickening is indicated by the shaded area. c) Concentric remodelling of LV with increased deposits of myocardial TGs documented by the relationship of myocardial lipids and concentricity index measured as a ratio of LV mass and volume. Normal levels of concentricity index are indicated by the shaded area. Reproduced and modified from [42] with permission from the publisher.

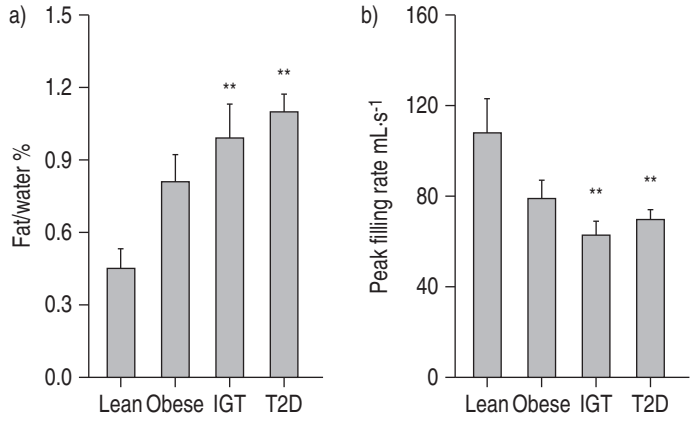


**Figure 3.** Obese patients with metabolic syndrome have elevated myocardial triglyceride (TG) levels and impaired filling rate of the left ventricle compared with lean individuals. a) Myocardial TG levels are significantly elevated in obese patients with impaired glucose tolerance (IGT; mean±SD body mass index (BMI) 31±6 kg·m$^{-2}$) and overt diabetes (T2D; BMI 34±7 kg·m$^{-2}$) compared with lean normoglycaemic individuals (BMI 23±2 kg·m$^{-2}$). Obese patients without glucose intolerance or diabetes had a BMI of 32±5 kg·m$^{-2}$. b) Diastolic function, measured as an early peak filling rate, was reduced in individuals with IGT and T2D. **: $p<0.01$. Reproduced and modified from [45] with permission from the publisher.

When looking specifically at pulmonary haemodynamics obtained invasively, a study of 40 moderately to severely obese patients found that 25% had normal $P_{pa}$ at rest and with exercise, another 50% had normal pressures at rest with exercise-induced elevation of $P_{pa}$, and 25% had elevations at rest and with exercise [51]. In all cases, elevated wedge pressures accompanied the elevations in $P_{pa}$.

When the pulmonary venous pressure rises above a critical level, pulmonary oedema will accumulate due to increased pulmonary capillary pressure. A marked increase in lymphatic drainage occurs in the lungs of patients with chronic elevations in pulmonary venous pressure, a protective mechanism to minimise the effects of the accumulating fluid on the pulmonary interstitium. Thus, some patients can accommodate marked elevations in left atrial and pulmonary venous pressures with little or no pulmonary oedema. In many, the ejection fraction is normal, the left heart is hypertrophied, and the transpulmonary gradient and PVR are within normal limits ($\leqslant$12 mmHg or $\leqslant$3 Wood units, respectively) [52]. These patients are categorised as having pulmonary venous hypertension in the setting of HFPEF.

Pulmonary venous hypertension is highly associated with the metabolic syndrome. In a single-centre study evaluating 122 consecutive patients referred for diagnosis and treatment of PH, patients with pulmonary venous hypertension had a higher frequency of hypertension, obesity, diabetes mellitus and hyperlipidaemia when compared with PAH patients [15]. Two or more features of the metabolic syndrome were found in 94.1% of patients with pulmonary venous hypertension compared with 34.3% of patients with PAH

($p<0.001$). PH was substantial, but less severe overall, in patients with pulmonary venous hypertension compared to those with PAH.

In a subgroup of patients with HFPEF, $P_{pa}$ rises above what would be expected based on passive mechanisms alone, and is commonly referred to as disproportionate or reactive pressure elevation and signified as PH-HFPEF. The haemodynamics of these patients are characterised by both an increase in the transpulmonary gradient (mean $P_{pa}$ – mean pulmonary artery wedge pressure) >12 mmHg and an increase in PVR (>3 Wood units) [53]. Similar to increased lymphatic drainage, this secondary reaction may also protect against pulmonary oedema by posing a pre-capillary resistance that reduces pressure applied to the pulmonary capillary bed. However, these reactive changes often progress beyond a protective level and can result in marked elevations in $P_{pa}$ (fig. 4). The prevalence of this condition among patients with HFPEF has not been firmly established, but one population-based study found that of 244 patients with a history of heart failure and a normal LV ejection fraction on echocardiography, 83% had an estimated pulmonary artery systolic pressure over 35 mmHg, 25% had a pulmonary artery systolic pressure over 48 mmHg and approximately 10% had a pulmonary artery systolic pressure over 60 mmHg [54]. Lacking RHC data, these authors were unable to derive firm estimations, but the echocardiographic data suggest that less than a quarter of HFPEF patients have PH-HFPEF at any one time and probably less than 10% have severe PH. Unfortunately, these authors did not present data on BMI, so the impact of obesity on the prevalence of HFPEF and PH-HFPEF remains largely unknown.

Although these prevalence data suggest that only a minority of HFPEF patients have PH-HFPEF at any one time, it is likely that many more patients go through a progression from HFPEF to PH-HFPEF. If the $P_{pa}$ rises excessively, the RV will fail with a concomitant rise in the right atrial pressure (right atrial hypertension; fig. 4) and drop in cardiac output. Importantly, the increase in right atrial pressure is viewed as the final step in the progression of pulmonary venous hypertension to right heart failure [55]. If the vasculopathy has reached an irreversible or "fixed" stage, normalisation of the left atrial and pulmonary venous pressures (as by normalisation of the $P_{pcw}$) will eliminate the passive component of the PH, but not the reactive vasculopathy. While there are no data to suggest that improvement in left filling pressures in the setting of diastolic dysfunction leads to gradual improvement in the reactive vasculopathy, evidence from patients with systolic left heart failure indicates that treatment with a LV assist device improves substantially, or even normalises, the so-called fixed PVR over a period of weeks to months [56].

Histologically, patients with reactive PH have thickening of the pulmonary veins, as well as a proliferative occlusive vasculopathy in the small

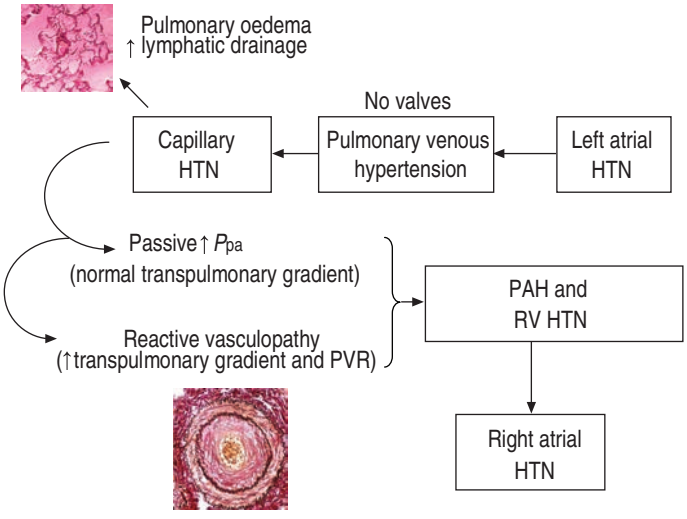


**Figure 4.** Pathophysiology of pulmonary venous hypertension and reactive pulmonary vasculopathy. In the setting of increased left atrial pressure, the absence of valves in the pulmonary veins translates into pulmonary venous hypertension, which, in turn causes a passive increase in the pulmonary arterial pressure ($P_{pa}$) while the transpulmonary gradient remains normal. If the left atrial and pulmonary venous pressures fall, $P_{pa}$ will decrease as well. Some patients with pulmonary venous hypertension develop a reactive pulmonary vasculopathy. The result is an increase in the transpulmonary gradient and pulmonary vascular resistance (PVR) with worsening of the pulmonary arterial hypertension (PAH). Right atrial hypertension occurs when the right ventricle (RV) fails. HTN: hypertension.

pulmonary arteries and arterioles, similar to that seen in patients with PAH (WHO group 1) disease [14]. The pathophysiology of the reactive vasculopathy is poorly understood, but is thought to involve many of the same molecular pathways as remodelling in IPAH, including pro-inflammatory cytokines, overexpression of endothelin, and suppression of the release of nitric oxide (NO) and prostacyclins in the face of endothelial cell dysfunction [57].

In addition to the reactive vasculopathy described above, some obese patients with LV diastolic dysfunction present with an atypical profile compared to those with classic pulmonary venous hypertension, in that the right atrial pressure is elevated out of proportion to the $P_{pa}$ and RV systolic pressure [58, 59]. Simultaneous pressure measurements in the RV and LV reveal a restrictive physiology with close tracking of the LV and RV diastolic pressures, and concordant changes in the LV and RV systolic pressures (fig. 5). We speculate that the restrictive physiology is due to the infiltrative process by fatty deposition, analogous to that seen in patients with cardiac amyloidosis. This explains the simultaneous increase in both the right and left atrial pressures even when biventricular systolic pressure is preserved.

In summary, the effects of obesity on the pulmonary vasculature are manifold and quite variable between individuals. The increase in inflammatory mediators circulating in obese individuals probably contributes to vasoactive and structural responses of the pulmonary vessels. However, effects of obesity on LV function are probably more important in pathogenesis, initially producing a passive increase in $P_{pa}$. Later, in a substantial minority of patients, a reactive component develops that increases PVR, and some of these patients develop sufficient PH to cause right heart failure. Cardiomyopathy with a restrictive physiology has been described in some obese individuals. The specific mechanisms involved are not well understood, and much of this paradigm is based on patients with PH related to left heart failure, irrespective of the presence of obesity. Undoubtedly, sleep disordered breathing with intermittent or sustained hypoxia is a major contributor in many obese patients, and genetic factors are certainly involved as well.

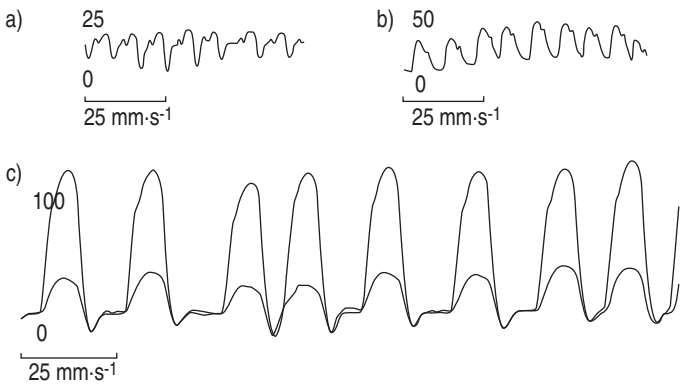


**Figure 5.** Obesity-associated restrictive cardiomyopathy. Haemodynamic evaluation of an obese individual revealed a mean right atrial pressure of 18 mmHg, pulmonary arterial pressure ($P_{pa}$) of 55/28 mmHg (mean 37 mmHg) and mean pulmonary capillary wedge pressure of 19 mmHg. The transpulmonary gradient was mildly elevated at 18 mmHg. The right atrial pressure is increased out of proportion to the $P_{pa}$. The simultaneous right ventricular (RV) and left ventricular (LV) pressure tracings reveal close tracking of the diastolic pressure in both ventricles, changes consistent with restrictive physiology. The patient had preserved RV and LV systolic function determined by echocardiography. The patient's cardiac rhythm was atrial fibrillation. a) Right atrial pressure; b) $P_{pa}$; c) RV/LV pressure.

## Treatment options for PH due to LV diastolic dysfunction in obese patients

Weight loss brings benefits in improving the function of all organs affected by excess fat, such as the heart, liver and pancreas. Animal studies suggest that treatments that prevent the deposition of lipid appear to prevent cardiac lipotoxicity [36]. Moreover, data from humans suggests that weight loss improves left heart function by favourable alterations in LV loading conditions and probably by decreasing the cardiac fat content (fig. 6) [60]. Although there are no formal studies looking at pulmonary haemodynamics in patients who have undergone treatment for obesity, it is safe to say that by improving left heart function and filling pressures, pulmonary venous pressure will also improve.

Such measures include: diet, which decreases lipid influx; coupled with exercise, which increases fatty acid oxidation; bariatric surgery [32, 61]; and more investigational approaches, such as leptin [62] and PPAR agonists [63].

Implementing a healthy lifestyle cannot be overemphasised as a useful therapeutic strategy. Exercise and diet programmes improve overall conditioning and sustained weight loss can be very effective at improving cardiac function. Although patients should be selected carefully to exclude those at excessive surgical risk, significantly reduced $P_{pa}$ has been observed following bariatric surgery in PH patients. Pharmacological approaches to the therapy of LV diastolic dysfunction have been disappointing to date, so systemic blood pressure control and optimisation of fluid volume are the current lynchpins of therapy [64]. Therapies should also be directed at comorbidities associated with the metabolic syndrome, such as tight control of blood sugar, and treatment of dyslipidaemias and associated coronary artery disease. Sleep apnoea should be sought and treated in patients with LV diastolic dysfunction. Although data pertaining specifically to obese patients with PH are lacking, continuous positive airway pressure (CPAP) for a cohort of severe sleep apnoea patients showed a significant improvement in pulmonary haemodynamics after 4 months, especially those with greater baseline $P_{pa}$ elevation, which was thought to be related to improved endothelial function [65].

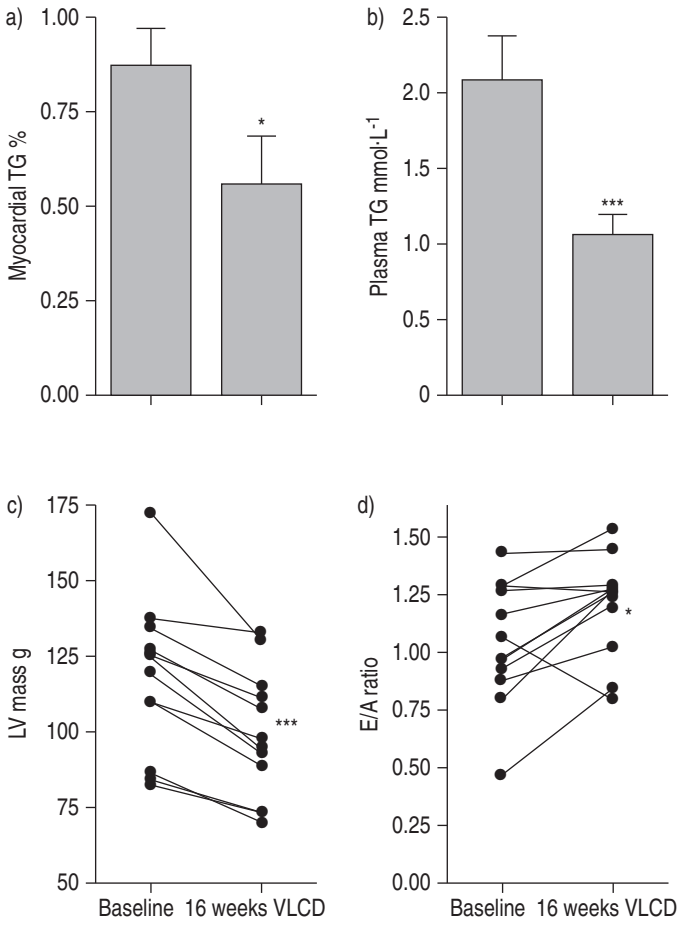


**Figure 6.** Changes in obese individuals after 16 weeks of a very low-calorie diet (VLCD) (450 kcal·day$^{-1}$) to achieve substantial weight loss. Individuals improved their body mass index from 35.6±1.2 kg·m$^{-2}$ at baseline to 27.5±1.3 kg·m$^{-2}$ after the intervention period. a) Myocardial and b) plasma triglyceride (TG) improved significantly. Data are presented as mean±SEM. Improvements in c) left ventricular (LV) mass and d) the ratio between the early filling phase and the atrial filling phase (E/A ratio) on VLCD. *: $p<0.05$; ***: $p<0.001$. Reproduced and modified from [60] with permission from the publisher.

At the present time, other effective treatments to reverse reactive pulmonary vasculopathy in the setting of obesity-related cardiac dysfunction are largely unexplored. Preliminary evidence in non-obese patients with HFPEF suggests that phosphodiesterase type-5 inhibitors (PDE-5 I), such as sildenafil, may have salutary effects on the PH associated with LV systolic [66] and diastolic dysfunction [67], but results from an ongoing larger randomised trial are still pending.

## PH in patients with OHS

OHS is an entity described in patients with significant obesity and is characterised by hypersomnolence, dyspnoea and resting hypoxaemia [67]. In addition to chronic hypoxaemia, patients with OHS have chronic, compensated, hypercapnic respiratory acidosis. In severe cases,

chronic hypoxaemia is associated with elevation of pulmonary pressures and the development of cor pulmonale [69]. Most patients with OHS have obstructive sleep apnoea (OSA), although the reverse is not true. These obese patients frequently demonstrate both nocturnal obstructive events and diurnal hypoventilation, probably secondary to a combination of increased respiratory impedance contributing to greater work of breathing as well as an acquired reduction in respiratory drive [70].

The occurrence of PH in the setting of ventilatory impairment, which leads to alveolar hypoxia, is currently classified as PH of WHO group 3 [51]. While OSA may cause mild elevations in $P_{pa}$, the presence of OHS has been associated with more significant PH and the prevalence of PH is greater in OHS than in OSA [71]. In an observational study of 50 patients with OSA, patients with cor pulmonale had more severe nocturnal and daytime hypoxaemia; nocturnal hypoxaemia in the absence of daytime hypoxaemia was not associated with cor pulmonale, suggesting that prolonged hypoxaemia was necessary to cause PH [72]. However, even brief intermittent periods of hypoxia, as may occur during sleep disordered breathing, have been shown to produce PH in animals [73].

Alveolar hypoxia with consequent hypoxic pulmonary vasoconstriction is thought to be the main mechanism responsible for the development of PH in OHS. In support of this idea, $P_{pa}$ correlates inversely with oxygen saturation in patients with OSA [74]. In reality, though, the mechanisms responsible for PH in the setting of OHS are probably multifactorial, and the occurrence of obesity cardiomyopathy, as described earlier, and increased incidence of systemic hypertension with HFPEF features may contribute to the development of a pulmonary vasculopathy. Other possible mechanisms that have been posited in PH associated with sleep disordered breathing include hypercapnia and decreased intrathoracic pressure [74, 75].

As the mechanisms responsible for the development of PH in OHS are multifactorial, PH treatment requires a complex approach. CPAP is used to improve nocturnal hypoxaemia in patients with OSA. Bilevel positive airway pressure (PAP) or adaptive servoventilation (ASV) may be helpful in patients with central apnoeas or failures to respond to CPAP alone [76, 77].

Although very few studies have examined the effect of CPAP on PH in sleep disordered breathing, some have shown improvements in systolic and mean $P_{pa}$ after 3–4 months of CPAP [65, 78], as well as improvement in RV function in a small group of patients [79] . The largest treatment effects have been noted in patients with elevated $P_{pa}$ prior to therapy. Anti-hypertensive therapy is geared towards LV diastolic dysfunction. Oxygen therapy is used for nocturnal hypoxaemia that is unresponsive to PAP therapy, or daytime hypoxaemia. Lastly, weight loss is beneficial. Loss of as little as 10 kg in patients with OSA and OHS has been shown to significantly reduce daytime hypercarbia, suggesting an improvement in ventilatory efficiency [80].

## Conclusions

The link between obesity and pulmonary vascular disease manifests itself in multiple ways. First, obesity and/or insulin resistance are thought to exacerbate the pulmonary vascular remodelling seen in PAH by means of inflammatory signalling pathways that are upregulated in obesity. Evidence is also accumulating to suggest that treatment of insulin resistance improves the obesity-related pulmonary vasculopathy. Secondly, obesity is associated with cardiac dysfunction due to increased lipid content and decreased fatty acid oxidation in the myocardium, perhaps related to accumulation of fatty acid in cardiomyocytes. This promotes LV diastolic dysfunction, predisposing to restrictive cardiomyopathy. The diminished LV diastolic compliance elevates pulmonary venous pressure; $P_{pa}$ then rises passively to maintain the transpulmonary gradient and, thereby, blood flow. In some patients, a reactive pre-capillary vasculopathy increases PVR and the transpulmonary gradient, sometimes causing severe PH and right heart failure. Thirdly, the presence of OHS and chronic alveolar hypoxia in severely obese patients predisposes to the development of PH and cor pulmonale. Current therapy includes optimal control of blood pressure and fluid volume, treatment of associated comorbidities, and diet and exercise with the

goal of weight loss. As we continue to learn more about the pathophysiology of obesity and associated conditions, understanding the physiological and molecular mechanisms underlying pulmonary vascular adaptations and maladaptations in the setting of obesity will be crucial to finding effective therapies.

### *Statement of Interest*

None declared.

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# Chapter 17

# Pregnancy and birth control in pulmonary hypertension

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**SUMMARY: Pulmonary arterial hypertension (PAH) most commonly occurs in females of childbearing age. Specific advanced therapies have been developed for PAH during the last decade that have improved quality of life and outcome for patients with PAH. However, despite these recent advances, pregnancy in females with PAH is associated with a high maternal mortality. Therefore, current guidelines strongly discourage pregnancy and recommend an effective method of contraception in females of childbearing age with PAH. If this fails, early pregnancy termination is advised. Those patients who choose to continue with the pregnancy must be treated early with targeted PAH therapies including prostanoids and/or phosphodiesterase type-5 inhibitors (PDE-5 I). In addition, the care of the pregnant females with PAH requires a highly planned, multidisciplinary approach, preferably in a dedicated pulmonary hypertension (PH) referral centre. This allows formulation of an agreed and documented management strategy for planned delivery and post-partum monitoring.**

**KEYWORDS: Hypertension, pregnancy, pulmonary, right heart failure**

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Pulmonary arterial hypertension (PAH) is a disease characterised by progressive obstruction of the pulmonary arterial vascular bed, leading to elevated pulmonary vascular resistance (PVR) and right heart failure if not treated adequately. Although it is still not possible to cure this disease, during the last decade therapeutic approaches on this devastating disorder have made remarkable progress. Nowadays, patients with PAH are treated with prostanoids, endothelin receptor antagonists (ERAs) and phosphodiesterase type-5 inhibitors (PDE-5 I), which have led to improvements in haemodynamics, exercise capacity and outcome [1–3].

PAH affects males and females of all ages, but it is predominantly seen in young females [4, 5]. Therefore, the management of birth control is a relevant and prevailing topic in this patient population. It is well known that pregnancy bears an enormous risk for patients with PAH [6]. Consistent with this, the current guidelines explicitly recommend avoiding or terminating early pregnancy in patients with PAH [7, 8].

Nevertheless, it is of particular importance to focus on the management of pregnancy as there will always be patients who, willingly or by accident, become pregnant against medical advice, and there is a certain number of patients being diagnosed with PAH during pregnancy [9]. Aside from this, recent case series have reported better outcomes of pregnancies in females with PAH in the modern management era, particularly in patients with well-controlled PAH and so-called responders (*i.e.* patients with vasoreactivity responding to calcium channel blockers (CCBs)) [9, 10].

The question is repeatedly raised of whether, considering the improvement in medical therapy and outcomes, the restricted directions of the guidelines have to be modified, as the possibility of giving birth to a child is often of great value to those patients. This question can still not be answered entirely as, despite the improved results seen recently, pregnancy still carries a high risk in these patients and data on long-term outcome of these individuals are still lacking.

In this chapter, we give an overview on the current data on the management of pregnant patients with PAH.

## Epidemiology and prognosis: maternal and fetal outcomes

Pregnancy is associated with an enormous risk and high mortality for patients with PAH and their offspring. The management of this disease has changed considerably during the last few years, which parallels improving mortality rates reported in recent reports [10–12].

In 1979, GLEICHER *et al.* [13] reported a mortality of 52% in a series of 70 pregnancies in patients with Eisenmenger's syndrome, with perinatal mortality of the infants of 28% and growth retardation in almost one-third of the neonates.

Another retrospective review study was published in 1998 reporting on the management and outcome in pregnant females with pulmonary hypertension (PH) between 1978 and 1996, an era where no PAH-targeted therapy was available [6]. This study found maternal mortality rates of 36% in patients with Eisenmenger's syndrome, of 30% in idiopathic pulmonary arterial hypertension (IPAH) and of 56% in patients with secondary PH (PAH associated with connective tissue disease (CTD), liver disease or drugs). Previous pregnancies, hospital admission, operative delivery, time of diagnosis and diastolic pulmonary artery pressure ($P_{pa}$) were maternal risk factors. Neonatal mortality was also high, ranging from 11% to 13% [6].

A recent systematic review on the outcomes of pregnancy in patients with PAH in the past decade (1997–2007) reported a lower overall maternal mortality compared with the previous era ($p=0.047$) [10]. Mortality was lower in all three subgroups investigated (from 30% to 17% in IPAH, 36% to 28% in Eisenmenger's syndrome and 56% to 33% in PAH of other aetiology). In this cohort, PAH-targeted therapies were used in 73% of the patients with PAH, 72% of the patients with IPAH, 52% of patients with PAH due to congenital heart disease (CHD) and in 47% of the patients with PAH of other aetiologies [10].

These findings were confirmed by prospective data published recently from our multinational registry with 13 participating centres examining the current outcome of pregnancies in patients with PAH. During a 3-year period, 26 pregnancies were reported. Three (12%) females died and one (4%) female diagnosed during pregnancy developed right heart failure requiring urgent heart/lung transplantation. There were eight abortions; two spontaneous and six induced. Both females with spontaneous abortions died whereas all females with induced abortions survived. 16 (62%) pregnancies were successful, *i.e.* the females delivered healthy babies without complications. These females had well-controlled PAH (mean $\pm$ SD PVR 500 $\pm$ 352 dyn·s·cm$^{-5}$); eight of them were long-term responders to CCBs. In contrast, the females who died or required transplantation had poorly controlled PAH (PVR 1,667 $\pm$ 209 dyn·s·cm$^{-5}$). According to these observations, maternal and fetal outcome seems to have improved, at least when PAH is well controlled and particularly in long-term responders to CCBs, but the risks are still high [9].

All available data indicate that even today, pregnancy is associated with a high mortality rate in PAH, but the results of the recent studies indicate that the outcome of pregnancies in PAH is improving. This may be attributable to the new pharmacological treatment options as well as to the better understanding of the disease and its management. The most recent data indicate that the risks associated with becoming pregnant in females with well-controlled disease and minor haemodynamic impairment may have declined. Nevertheless, these data must be confirmed by larger series before the general recommendation to avoid pregnancy in all patients with PAH can be reconsidered. In accordance with the current guidelines and with respect to the high mortality rates, pregnancy should still be avoided or terminated early in females with severe PAH.

## Physiological changes during pregnancy and delivery, and consequences in PAH

During pregnancy, manifold maternal physiological changes occur to fulfil the increased metabolic needs of both mother and fetus. As left ventricular (LV) mass [14], red cell mass [15], cardiac output and blood volume increase, systemic vascular resistance and blood pressure decrease [16]. Until reaching a maximum of 40–100% above normal between 28 and 34 weeks of gestation, the blood volume increases during pregnancy, whereas red cell mass increases up to 25% above normal [17–19]. This discrepancy explains the ''physiologic anaemia'' in pregnancy.

An increase of 30–50% in cardiac output can be observed, which is initially reached by a increase in stroke volume. This changes during later pregnancy and heart rate begins to increase. It accelerates from week 20 to a maximum in week 32–38, resulting in an average cardiac output of 8.7 $L \cdot min^{-1}$, staying high until 2–5 days post-partum. Intrapartum, a blood volume of approximately 500 mL per contraction is shifted from the uterus to the venous system [16, 20, 21]. Regarding respiratory changes, oxygen consumption increases, leaving respiratory rate unchanged.

Effects of progesterone and vasodilating mediators, such as nitric oxide (NO) and prostacyclin (prostaglandin $I_2$; $PGI_2$), lead to a decrease in peripheral vascular resistance and systemic blood pressure, with a drop in diastolic pressure of around 10%, returning to normal in the third trimester [16].

Due to the enlarging uterus, left axis deviation may appear on the ECG, and in mid-pregnancy, the vena cava and aorta may be compressed, which can lead to a reduction of venous return to the right ventricle. Renal blood flow and glomerular filtration rate increase during pregnancy, and increasing levels of renin and angiotensin lead to retention of salt and water. Pharmacokinetics of drugs may differ during pregnancy due to an excess of venous pooling. [16, 22]. A tendency toward hypercoagulability is seen during pregnancy, caused by a decrease in protein S, acquired protein C resistance and higher levels of thrombin [23], which may expose these patients to a higher risk of pulmonary embolism.

In summary, the physiological changes during pregnancy lead to an increased plasma volume and accelerated cardiac output that cannot be adequately processed/handled by the altered and obstructed pulmonary vasculature and the strained right ventricle of patients with PAH (fig. 1). This may even become more evident during labour and delivery, when the patient might be exposed to pain, acidosis, hypoxia and hypercapnia, resulting in further elevated PVR [24–26].

## Clinical presentation

Patients with PAH typically deteriorate at 20–24 weeks of gestation, when pregnancy-related haemodynamic changes are the most important [11]. Fatigue, worsening of dyspnoea, syncope and chest pain are the most frequently observed symptoms [27]. Patients are likely to be admitted antenatally mainly due to clinical deterioration, as is indicated in the US case series where IPAH led to a five-fold increase in antenatal hospitalisations [28]. Patients with Eisenmenger's syndrome are more

likely to have a pre-existing diagnosis prior to pregnancy, compared to those with IPAH [6, 10]. In the most recent case series, 55% of patients with IPAH were *de novo* presentations during pregnancy [10].

In this setting, dyspnoea, excessive peripheral oedema and weight gain, for example, may be considered as normal during pregnancy and diagnosis of PAH can easily be delayed.

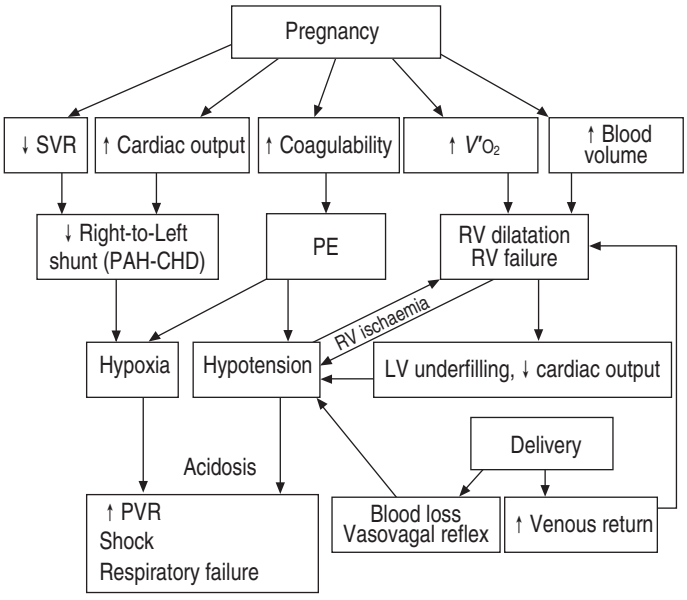


**Figure 1.** The physiological response to pregnancy in pulmonary hypertension. SVR: systemic vascular resistance; $V'_{O_2}$: oxygen uptake; PAH: pulmonary arterial hypertension; CHD: congenital heart disease; PE: pulmonary embolism; RV: right ventricular; LV: left ventricular; PVR: pulmonary vascular resistance. Reproduced and modified from [20] with permission from the publisher.

## Diagnosis of PH during pregnancy

As in the nonpregnancy setting, echocardiography is a very useful screening tool to detect patients with suspected PH. During pregnancy, however, it may be more difficult to view the inferior vena cava because of the effects of the gravid uterus. Right atrial pressure ($P_{ra}$) may therefore be overestimated [29]. A study of 11 critically ill obstetric patients, where echocardiography and right heart catheterisation (RHC) were performed simultaneously, showed a good correlation between the two techniques in the estimation of cardiac index, intracardiac pressures or systolic $P_{pa}$ [30]. A more recent study evaluated the correlation of estimated $P_{pa}$ by echocardiography with RHC measurements in pregnant females. The results again showed a good correlation between right ventricular systolic pressure estimated by echocardiography and $P_{pa}$ measured by RHC. However, in 30% of cases, RHC eliminated the diagnosis of PH when echocardiography suspected the presence of PH [29]. In a further study comparing the accuracy of echocardiography *versus* RHC in pregnant females with suspected PH, echocardiography similarly overestimated right ventricle systolic pressure in 30% of cases compared with RHC (59.6 *versus* 54.8 mmHg, $p<0.004$). In addition, 32% of the patients had PH when estimated by echocardiography, but had normal $P_{pa}$ on subsequent RHC [31]. Therefore, RHC remains the gold standard to confirm the presence of PH, to assess the severity of the disease and to guide treatment decisions, such as pregnancy interruption or preterm delivery. Moreover, ROBERTS and KEAST [32] have been able to provide some prognostic data on pregnant patients with PAH using RHC values demonstrating an improvement in survival with a cardiac index of over 4 $L \cdot min^{-1}$, $P_{ra}$ less than 10 mmHg and PVR less than 1,000 $dyn \cdot s \cdot cm^{-5}$ [32].

## Management of PH during pregnancy

### General measures and conventional therapy

Despite the observed reduction in mortality in the last decade, the maternal risk remains significant [9, 10]. Most PH specialists therefore strongly discourage pregnancy, giving specific contraceptive advice to females of childbearing age and advising termination of existing pregnancies when indicated, preferably before 22 weeks gestation. Females continuing with pregnancy should be assessed monthly, ideally in a PAH referral centre, and, in addition to full clinical evaluation, should undergo echocardiography [33]. Monitoring of fetal growth is

recommended to assess for intrauterine growth retardation (IUGR). General measures include limitation of physical activity to minimise additional cardiac demands. Periods of bed rest are therefore thought to be advisable to avoid additional strain.

Diuretics may be useful during pregnancy to relieve the increased intravascular volume and reduce hepatic congestion resulting from right ventricular (RV) failure. Furosemide is safe in pregnancy, and the dose may be escalated as required.

Lifelong anticoagulation is recommended in patients with IPAH to reduce the risk of *in situ* thrombosis and thromboembolism. These patients generally receive vitamin K antagonists (VKAs). However, VKAs are contraindicated during the first trimester as they may lead to fetal craniofacial malformations. Conversely, heparins are safe throughout pregnancy, although there are no current guidelines in terms of heparin dosage (thromboprophylaxis *versus* treatment dose) or management around the time of delivery. Therefore, current recommendations are to anticoagulate patients with PAH throughout pregnancy, usually with low molecular weight (LMW) heparin [11, 33, 34].

## PAH-specific therapy

Several case reports or case series and one prospective registry have described the successful use of pulmonary antiproliferative and vasodilator therapy in this patient population [9–11, 35–50]. Increased mortality has been associated with both severe PH and late diagnosis [6]; therefore, early treatment with PAH therapies is indicated. In the most recent large series, where 60% of patients were in New York Heart Association (NYHA) functional class III–IV during pregnancy, 72% of IPAH patients and 52% of those with CHD-PAH received specific PAH therapy during pregnancy [10].

### *Calcium channel blockers*

In those patients that have evidence of a positive vasoresponse to inhaled NO, high-dose CCBs are indicated [51], and both nifedipine and diltiazem are safe to use during pregnancy [52, 53]. Sometimes, in these "responders" to inhaled NO, high-dose CCBs may produce near-normalisation of $P_{pa}$ and RV function after long-term use [51]. A recent prospective registry showed successful pregnancies in all females who were positive responders, *i.e.* patients with a vasoreactive form of PH in whom haemodynamics become normal or almost normal with CCB therapy [9]. This patient group may be the only subgroup of PAH patients in whom pregnancy might be allowed to progress to term [9, 11, 53].

### *Prostanoids*

#### Epoprostenol

Intravenous epoprostenol ($PGI_2$) remains the first-line therapy for the most severe patients with PAH [7, 8]. Reproductive studies in rats and rabbits have shown no impaired fertility or fetal harm at 2.5–4.8 times the recommended human dose [34]. There have been several case reports documenting its successful use in pregnancy with no reported adverse fetal outcomes [9, 36, 37, 40, 42, 43, 47, 48, 53]. It has also been used to manage acute perioperative PH exacerbations without adverse events [11, 37, 44, 49, 54]. There remain, however, reported maternal deaths despite treatment with epoprostenol [49, 54], which may reflect delayed recognition and treatment when PAH presents in late pregnancy [35, 53], as well as the real risk of late maternal death despite maximal treatment.

#### Iloprost

Iloprost, delivered by inhalation, has been also used during pregnancy. There are conflicting reports of congenital anomalies following iloprost use in animal studies. However, there have been several successful pregnancies using inhaled iloprost in NYHA functional class II–III patients, which were described with no congenital abnormalities [9, 39, 41, 55].

### *Phosphodiesterase type-5 inhibitors*

Sildenafil is effective in PAH through a reduction in cyclic guanidine monophosphate (cGMP) breakdown, thus increasing the sensitivity of pulmonary vascular smooth muscle to NO. In addition, sildenafil causes uterine artery vasodilatation and has been shown to have beneficial

effects on myometrial thickness. There have been several reports of its successful use in pregnancies with PAH with no reported adverse fetal outcomes [9, 37, 45, 46]. There are no data on the safety and efficacy of tadalafil in pregnant females with PAH.

### *Endothelin receptor antagonists*

Endothelin-1 (ET-1) plays an important role in fetal development [56], and ERAs are potent teratogens in animal studies. Therefore, pregnancy must always be excluded prior to starting treatment with ERAs, and pregnant females stable on these agents should be switched to alternative agents.

## Current treatment recommendations

Establishment on prostanoid therapy is indicated as early as possible in patients that progress with pregnancy [11, 36, 41, 47]. Intravenous epoprostenol should be the recommended treatment for patients in NYHA functional class III–IV [11, 34, 40]. Nebulised iloprost [39, 41] or oral sildenafil [45, 46] may be suitable treatment options for patients in NYHA functional class II with more stable PAH. A proposed treatment algorithm is shown in figure 2.

## Peripartum and post-partum management

### *Method of delivery*

The timing and optimum mode of delivery (vaginal *versus* caesarean section) remains debated [6, 9–11, 33, 57–59]. Successful caesarean section and vaginal deliveries have both been reported [9–11, 35, 39, 47, 60–63]. In the US 2002–2004 report, 57.9% of IPAH cases were delivered by caesarean section compared with 31.1% in controls ($p<0.05$) [28]. Vaginal delivery is associated with fewer infections, and reduced blood loss and thromboembolic risk [64], although the latter is reduced with thromboprophylaxis. There are also less abrupt haemodynamic changes during vaginal delivery, particularly when assisted by effective analgesia. However, prolonged, difficult and painful labours can have detrimental pulmonary vascular effects [65]. Moreover, the proportion of premature deliveries is reported to be high (59–85%) in several studies [10, 11, 49, 54]. Therefore, the lack of predictable delivery time where the team can be fully prepared makes a case for the planned induction of labour. Elective caesarean section has the advantage of taking place during the day and avoiding the risk of an urgent caesarean section out of hours. The timing is usually 32–34 weeks for

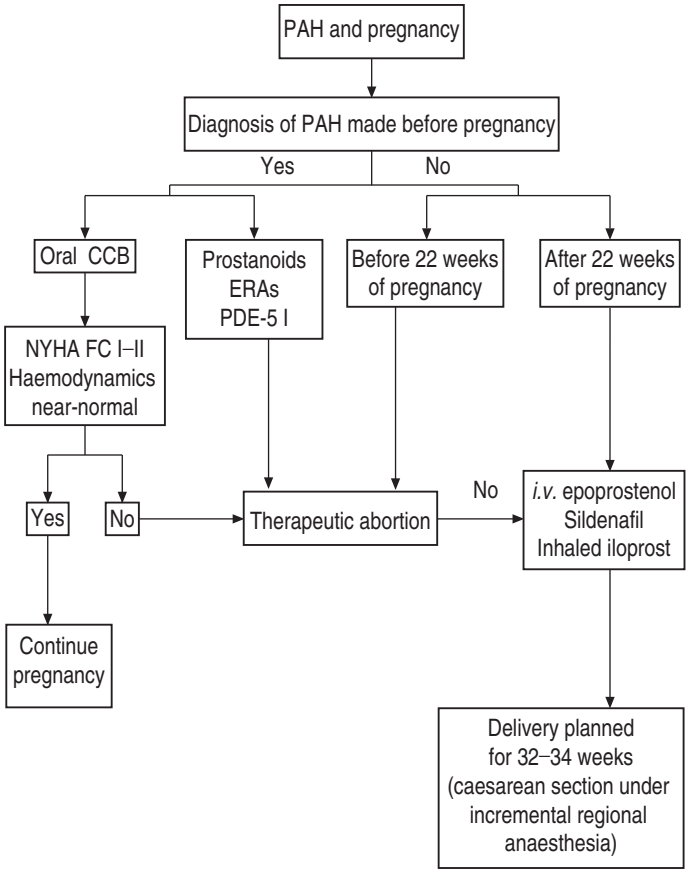


**Figure 2.** Algorithm for the management of pregnant females with pulmonary arterial hypertension (PAH). CCB: calcium channel blocker; ERA: endothelin receptor antagonist; PDE-5 I: phosphodiesterase type-5 inhibitors; NYHA: New York Heart Association; FC: functional class.

planned deliveries to allow sufficient fetal maturity while avoiding maternal physiological deterioration and unplanned emergency deliveries.

### *Peripartum monitoring*

Intra-operative monitoring at delivery is always advocated with ECG, pulse oximetry and invasive arterial blood pressure monitoring [35, 53, 61–63, 66]. Central venous pressure (CVP) [67] and a form of cardiac output monitoring are advisable to detect the onset of low cardiac output and increasing CVP, which are characteristic of RV failure. The use of a pulmonary arterial catheter is debated because of the increased risk of pulmonary artery thrombosis, rupture or perforation [68], and also of both atrial and ventricular arrhythmias in PAH [69, 70]. There is also no current evidence that pulmonary artery catheter use improves outcomes in parturients with PAH [6, 11].

### *Anaesthetic technique*

The haemodynamic principles of anaesthetic management in females with PAH are the maintenance of oxygenation, normovolaemia, normotension, minimising catecholamine surges with adequate analgesia and reducing ventricular preload in the immediate post-partum period. Deliveries by caesarean section may be performed under general anaesthesia [9, 11, 35, 60, 67] although there is an increasing body of evidence suggesting that caesarean section under incremental regional anaesthesia is preferable in these patients [11, 71]. A systematic review of all PAH pregnancies published between 1997 and 2007 found that parturient females who received general anaesthesia for caesarean section were at higher risk of death [10]. In patients where incremental regional anaesthesia techniques are used, however, the haemodynamic challenges appear to be reduced [11, 61, 72–75]. These techniques describe the use of gradual doses of epidural anaesthesia, with or without a small single spinal dose.

The use of neuraxial blockade therefore requires cessation of anticoagulation with LMW heparin. The potential additional bleeding risk due to the antiplatelet effects of *i.v.* prostacyclin should be considered, although as far as we are aware, there have been no reported cases of this potential complication when heparinisation is temporarily discontinued in the peripartum period [11, 40].

### *Post-partum management*

Most maternal deaths occur between 2 and 30 days following delivery [6], mostly due to RV failure. Contributing factors to RV failure include placental autotransfusion volume-loading a failing RV, excessive PVR due to any cause leading to PH exacerbation, adverse haemodynamic effects of oxytocin and thromboembolic events [37, 60, 76]. The increased risk should be anticipated by the multidisciplinary team. Current recommendations are to continue close maternal monitoring for at least 72 hours post-partum, ideally in an intensive care unit [11, 60, 64, 77].

The principles of management of RV failure always include minimisation of RV afterload and maintenance of appropriate RV pre-load with sufficient systemic vascular resistance for adequate coronary perfusion. In the setting of a PH exacerbation, the minimisation of RV afterload with maximal pulmonary vasodilator therapy is absolutely crucial. Therapies for post-partum PH exacerbations include inhaled NO [11, 35], *i.v.* epoprostenol [11, 36, 40] and inhaled iloprost [11, 37]. Systemic vasopressors and inotropes may also be needed, with dobutamine [37] being a good choice of inotrope as it increases contractility but not PVR/systemic vascvlar resistance ratio, and norepinephrine a commonly used vasopressor [78, 79]. Anticoagulation is widely indicated in the post-partum period. LMW heparin can usually be restarted 12 hours after delivery, in the absence of persistent bleeding.

## Birth control in PH

### Pregnancy termination

Therapeutic abortion should be offered, particularly when early deterioration occurs [7, 8]. The earlier the procedure can be performed, the lower the theoretical maternal risk. Maternal

counselling should always be offered [58, 80]. In one prospective registry of patients with PAH, six pregnancies were terminated in patients between 7 and 13 weeks without complications [9]. From other studies, perioperative mortality rates are reported to be up to 4–6% in females undergoing interruption of pregnancy [25]. Late surgical termination is certainly associated with increased haemodynamic challenge and risk [81]. Nonsurgical methods for late termination, such as the anti-progestogen RU486, may be an alternative, although this has not been described in this patient population.

### Contraception

Effective contraception is clearly very important in this patient group; however, it may be particularly challenging because of potential drug interactions. Furthermore, oestrogen-containing agents are usually contraindicated in females with PAH because of the increased risk of venous thromboembolism (VTE). Progestogen-only contraception is not thought to increase the risk of venous thrombosis, so is safer than oestrogens in this patient group. Desogestrel 75 µg (Cerazette®; Organon Laboratories Ltd, Hoddesdon, UK) is a new formulation of progestogen-only pill (POP) that has a 12-hour window if missed [58]. However, the p450 enzyme-inducing effect of bosentan reduces the efficacy of POPs. Therefore, hormonal contraceptives, including oral, injectable, transdermal and implantable contraceptives, should not be used as the sole means of contraception because these may not be effective in patients receiving bosentan.

Barrier contraceptive methods are safe but with an unpredictable effect. A levonorgestrel-releasing intrauterine device (Mirena®; Bayer AG, Leverkusen, Germany) is very effective but, rarely, leads to a vasovagal reaction when inserted, which may be poorly tolerated in the setting of severe PAH. A combination of two methods may also be proposed [58].

For emergency contraception, the commonly used agent, levonorgestrel (containing no oestrogens), is safe in patients with PAH. It is administered as a single dose and, when used within 72 hours of exposure, has a 1% failure rate [58].

### Sterilisation

Sterilisation can be performed at the time of caesarean section, avoiding the risk of a separate procedure; however, the failure rate is reportedly higher in this setting. The role of awake hysteroscopic sterilisation is not currently clear in PAH [82], but is an appealing alternative and would avoid the risks of general anaesthesia and laparoscopy in these patients.

## Conclusion

Despite the recent advances in the management of pregnant females with PAH, maternal mortality remains high. Therefore, pregnancy should continue to be strongly discouraged in patients with PAH. Patients who become pregnant should be informed of the high maternal risk of pregnancy and early termination, when possible, should be discussed. Those patients who choose to continue pregnancy should be treated early with PAH-targeted therapies including *i.v.* epoprostenol and/or sildenafil. In addition, the treatment and care of the pregnant female with PAH can be challenging and is best undertaken at PAH referral centres that can manage this unique state with a multidisciplinary team approach. This allows formulation of an agreed and documented management strategy for planned delivery and post-partum monitoring.

***Statement of Interest***
K.M. Olsson has received speaker and or consultant fees from Actelion and Pfizer. X. Jaïs has received speaker and/or consultant fees from Actelion, GSK, Lilly and Pfizer.

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# Chapter 18

# Anaesthesia and surgery in pulmonary hypertension: perioperative management

*Laura Price*, John Dick#, S. John Wort* and Brian Kavanagh¶*

**SUMMARY:** Pulmonary hypertension (PH) is an independent risk factor for perioperative complications, including death. Physiological challenges during anaesthesia and surgery can precipitate an increase in pulmonary vascular resistance (PVR) and/or worsen right ventricular (RV) function, which may lead to pulmonary hypertensive crises and acute RV failure, the cause of most perioperative complications and mortality. Certain types of cardiothoracic procedures are at increased risk of perioperative PH, with mortality related to RV failure exceeding 80%. In patients with pre-existing PH, retrospective single-centre studies suggest the mortality risk from general surgical procedures ranges from 7% to 18%, with a morbidity of 14–42%. Most studies are, however, limited by small numbers and the grouping of heterogeneous procedures and patient groups. The presence of pre-operative RV dysfunction, lower exercise tolerance and increased New York Heart Association (NYHA) functional class are pre-operative indicators of worse outcomes; operative factors include long duration or surgery, as well as high-risk or emergency surgery. Herein, perioperative management and planning, including management of PH crises, will be discussed.

**KEYWORDS:** Acute right ventricular failure, anaesthesia, perioperative management, pulmonary hypertension, pulmonary hypertensive crisis, surgery

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Pulmonary hypertension (PH) describes a range of conditions defined by a mean pulmonary artery pressure ($P_{pa}$) exceeding 25 mmHg. Pulmonary arterial hypertension (PAH) also requires a pulmonary capillary wedge pressure ($P_{pcw}$) of less than 15 mmHg [1]. PAH includes idiopathic PAH (IPAH), which is a rare condition with a prevalence of up to 15 cases per 1 million adults [2]. Other forms of PAH are more common and include PAH associated with congenital heart disease (CHD), connective tissue disease (CTD)-associated PAH, *e.g.* lupus (observed in up

to 14% of systemic lupus erythematosus (SLE) patients [3]), and PAH associated with HIV (0.5% of HIV patients have PAH) [4]. Ultimately, patients with PAH develop right ventricle (RV) dilatation and failure, the inevitable cause of death despite recent treatment advances.

PH is classified in to five broad groups with PAH being group 1 (table 1, chapter 2) [5, 6]. Other subtypes include PH due to left heart disease (group 2) or lung disease/hypoxia (group 3). Groups 2 and 3 are more prevalent than group 1 (PAH) but are usually less severe. PH may have several contributing causes in a single patient. For example, a patient with sarcoidosis might have PH due to PAH, as well as PH associated with left-sided heart disease (*e.g.* myocardial fibrosis) and/or interstitial lung disease (ILD). It is important to identify the contributors to PH as they may have individual treatment implications, even though the final common PH pathway may be elevated RV afterload regardless of the contributing cause(s).

Patients with pre-existing PAH are one of the patient groups at highest risk during anaesthesia and surgery. The main risk is precipitation of potentially fatal acute RV failure. With recent improvements in survival [7], patients with PAH are increasingly likely to undergo both diagnostic and therapeutic procedures. Due to the rare nature of the disease, however, most studies of surgery and anaesthesia in these patients have combined group 1 patients with other PH subtypes; there are few studies of PAH patients alone. Similarly, there are data for some, but not all, procedures that are likely to be performed in PH patients. Additionally, there are certain procedures, especially within the field of cardiothoracic surgery, where patients with degrees of underlying pulmonary vascular disease develop "post-operative" or "perioperative" PH as a relatively common short-term complication.

The principle aim of this chapter is to enhance the effectiveness of consultation among PH physicians with anaesthetic and surgical teams in the perioperative management of these challenging patients. Therefore, we will first outline the unique pathophysiological challenges faced by PH patients in the perioperative setting and then describe the available studies of patients with pre-existing PAH/PH undergoing specific procedures. Finally, we will summarise general management strategies based on current knowledge, and outline areas where knowledge is particularly limited.

## Pathophysiology of PH and RV failure

Normal pulmonary endothelium maintains the balance of vascular tone through the production of pulmonary vasodilating substances (*i.e.* nitric oxide (NO), prostaglandin (PG)$I_2$ (prostacyclin) and vasoconstrictors such as endothelin-1 (ET-1) (predominantly by endothelial cells)) and serotonin from platelet granules. In PAH, an imbalance of these mediators contributes to pulmonary vasoconstriction, vascular cell proliferation and thrombus formation [8], resulting in vessel remodelling, *i.e.* pulmonary artery medial hypertrophy, adventitial thickening and neointimal lesions. The resulting vessel narrowing reduces the cross-sectional area of the pulmonary vascular bed, increasing pulmonary vascular resistance (PVR). This initially leads to protective RV remodelling and hypertrophy. Patients with PAH can tolerate high PVR with normal RV function for a certain time but, ultimately, RV failure develops, which is characterised by dilatation of right-sided heart chambers and tricuspid regurgitation. The dilated RV causes an "internal tamponade" effect whereby the interventricular septum bulges and compresses the left ventricle (LV) (interventricular dependence) reducing systemic ventricular function [9, 10]. Coronary perfusion of the RV, present under normal circumstances during systole and diastole, occurs only in diastole because RV systolic pressure is at systemic levels. In addition, coronary flow during diastole is reduced because the elevated RV diastolic pressure (due to RV failure) reduces the coronary perfusion gradient and the diastolic time is shortened if the heart rate is increased. If untreated, an ongoing downward spiral of failing biventricular function further worsens coronary blood flow and ultimately leads to cardiovascular collapse and death [11].

Pulmonary vascular remodelling reduces the vessel capacitance (*i.e.* compliance) thereby limiting the unique ability to dilate and "recruit" vasculature in order to maintain low pulmonary vascular pressure, which is essential to protect the fragile alveolar–capillary barrier [12]. Under normal

circumstances, vascular recruitment allows for increases in cardiac output, such as those that occur during sympathetic stimulation (*e.g.* exercise and surgical stress), and increased blood volume (*e.g.* pregnancy) without increasing RV afterload. Thus, with impaired vascular capacitance, patients with PH may develop marked increases in RV afterload if cardiac output increases.

Clinical presentation of RV failure in PH patients may range from chronic effects of elevated systemic venous pressure (*e.g.* peripheral oedema, hepatic congestion and ascites) to the more dramatic syndrome of acute RV failure, which may follow a "pulmonary hypertensive crisis" (fig. 1). When not anticipated, these may be difficult clinical diagnoses to make and challenging to treat. A PH crisis describes a hyper-acute increase of systolic pulmonary pressure (>50% of systemic pressure) due to any cause [13]. Acute cor pulmonale (or "acute right heart syndrome") describes acute RV failure in the setting of acutely elevated afterload, *e.g.* due to acute pulmonary embolism, acute lung injury or the effects of positive pressure ventilation [14].

## Perioperative RV failure

Acute RV failure may be precipitated by several factors in PH patients in the perioperative setting (table 1). For example, a critically reduced systemic blood pressure following induction of

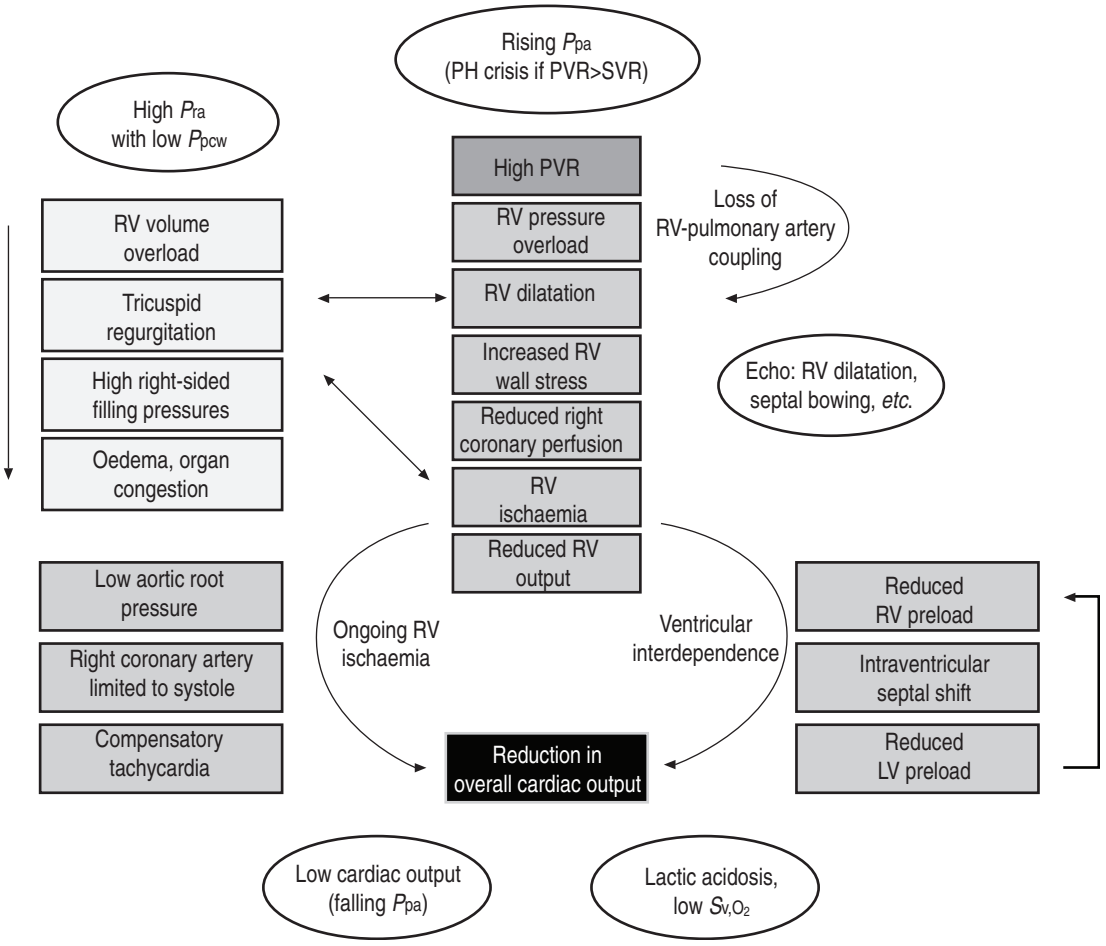


**Figure 1.** Schematic diagram illustrating the pathophysiology of acute right ventricular (RV) failure in the setting of pulmonary hypertension (PH). The corresponding clinical signs are shown in the bubbles. $P_{ra}$: right atrial pressure; $P_{pcw}$: pulmonary capillary wedge pressure; $P_{pa}$: pulmonary artery pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; $S_{v,O_2}$: mixed venous oxygen saturation; Echo: echocardiography; LV: left ventricular.

**Table 1.** Potential adverse impact of perioperative factors on pulmonary vascular/right ventricular (RV) function

| Anaesthetic factors | Surgical factors |
|---|---|
| **Laryngoscopy: extubation** | **Surgical stress and pain** |
| Sympathetic stimulation | Sympathetic stimulation |
| Tachycardia | Tachycardia |
| **Hypotension** | **Surgical mechanics** |
| General *versus* regional anaesthesia | One-lung ventilation |
| **Positive pressure ventilation** | Positioning, *e.g.* Trendelenberg |
| High plateau pressure | Pneumoperitoneum |
| High partial pressure of carbon dioxide | **Hypoxia (HPV) and acidosis** |
| **Adverse drug effects** | Cytokine release |
| Volume overload, *i.e.* fluids | Endothelial dysfunction and CPB |
| Drugs to avoid: protamine and prostaglandin $F_{2\alpha}$ (increase PVR) | **Fluid shifts during pregnancy** |
| | **Early/late hypotension** |
| | Haemorrhage |
| | Sepsis |

PVR: pulmonary vascular resistance; HPV: hypoxic pulmonary vasoconstriction; CPB: cardiopulmonary bypass. Many perioperative factors may precipitate a pulmonary hypertension crisis [1] and/or worsen RV function directly [2]. Factors increasing PVR include sympathetic stimuli, such as pain and airway instrumentation, endothelial activation (cytokine and endothelin-1 release), effects of hypoxia, hypercapnic acidosis and positive pressure ventilation. Anaesthetic drugs that may increase PVR include ketamine (causes tachycardia and very minor increases in mean pulmonary artery pressure [15]) and some inhalational agents, including desflurane [16]. The inhalational anaesthetic agent nitrous oxide impairs endothelial function [17] and is associated with adverse cardiovascular outcomes [18]. Of the factors that may also worsen RV function, all *i.v.* anaesthetic-induction agents depress myocardial function and reduce systemic vascular resistance to varying degrees [19].



anaesthesia may reduce right coronary perfusion pressure, inducing RV ischaemia, especially if compounded by preload inadequacy (*e.g.* hypovolaemia) or excess (*e.g.* excessive intravenous fluids). When combined with any cause of an increased PVR (*e.g.* sympathetic stimulation from airway instrumentation [20] or an episode of alveolar hypoxia), a PH crisis may result, with rapidly progressive RV ischaemia and failure. This may be compounded by other factors such as dysrhythmias.

In addition to tachycardia, bradycardia can also impair cardiac output and, therefore, RV coronary perfusion as the stroke volume in PH is relatively fixed and the cardiac output (*i.e.* stroke volume × heart rate) is critically dependent on an adequate heart rate. In addition, the negative inotropic effect of many anaesthetic agents or increased PVR due to high ventilator pressures can contribute [21]. Abdominal insufflation with carbon dioxide during laparoscopic surgery may cause acute hypercapnic acidosis resulting in increased PVR and heart rate, and may lower RV preload through abdominal distension [22]. It is also likely that endothelial function may be modulated, directly or indirectly, by the release of vasoactive substances induced by inflammation during or after surgery [23], notably following cardiopulmonary bypass (CPB).

## PH associated with cardiothoracic surgery

Severe RV failure in the setting of cardiothoracic surgery is associated with an in-hospital mortality of 44–86% [24], especially with certain procedures (table 2). This important topic is well reviewed elsewhere [25] but we will briefly discuss it as it has obvious relevance to PH in the setting of other types of surgery.

Perioperative PH in the setting of cardiothoracic surgery occurs in two settings: the use of CPB and consequences of lung resection. A relatively novel context is pulmonary endarterectomy for chronic thromboembolic PH (CTEPH). CPB induces endothelial dysfunction and inflammation resulting in the loss of NO production [26], and patients undergoing CPB who receive reversal of heparin with protamine can develop precipitous elevations in PVR due to thromboxane $A_2$ release

by circulating protamine–heparin complexes [27]. Finally, one-lung ventilation results in a temporary increase in PVR due to lung compression; lung resection is associated with a loss of lung vessel cross-sectional area. Both of these phenomena may exacerbate PH crises in patients with pre-existing PH.

**Table 2.** Cardiothoracic procedures associated with a high risk of perioperative pulmonary hypertension and right ventricular failure

| |
|---|
| **Cardiac surgery** |
| Corrective congenital cardiac surgery, especially for total anomalous pulmonary venous correction, transposition of the great arteries and ventricular septal defects |
| Heart transplantation surgery |
| Valve replacement surgery (mitral much greater than aortic) |
| Left ventricular assist device insertion |
| **Thoracic surgery** |
| Pneumonectomy |
| Pulmonary endarterectomy |

In adults, the presence of PH is an independent risk factor for mortality in cardiac surgery [28–30]. For example, in mitral valve surgery, pre-operative PH is an independent risk factor for perioperative RV failure and because the PH is progressive, it has been suggested that patients might benefit from earlier surgery [30]. RV failure may also occur in up to 39% of patients requiring LV assist device support [31].

Heart transplantation can be particularly challenging because of the mismatch between the elevated PVR in the recipient's lungs and the compromised RV function in the donor heart. In the recipient's lungs, the PVR is chronically elevated and this will be unchanged, or may be increased because of the effects of CPB on the vascular endothelium. The previously healthy donor RV, which had functioned at low pressures (with low PVR), has two challenges: 1) the pressures required to perfuse the recipient's lungs are greater than can readily be generated; and 2) the heart is recovering from ischaemic storage (between organ retrieval and implantation) and thus the RV is especially compromised. This does not result in a PH crisis because the RV cannot generate high pressure; nonetheless, RV failure can develop and the condition is termed RV afterload mismatch.

Children undergoing surgery for CHD can be susceptible to PH crises, mainly because long-standing left-to-right shunt (*e.g.* ventricular septal defect) causes increased pulmonary vascular reactivity which may be worsened following surgery and CPB. Although inhaled NO is effective in treating this condition [32], the problem is becoming less frequent in countries where such lesions are corrected earlier. Indeed, while PH complicated the post-operative care of 16% of one cohort prior to 1994 [13], in a more recent series this occurred in 2% of children [33]. Although it is becoming less common, PH following cardiac surgery in children remains an important cause of prolonged intensive care unit (ICU) stay [34].

## Diagnostic procedures in patients with pre-existing PH

Diagnostic procedures such as flexible bronchoscopy and lung biopsy may be indicated in PH patients, albeit very rarely. In general, these should be avoided if possible.

### Flexible bronchoscopy

PH may increase the risk of bronchoscopy-associated bleeding, hypoxia and haemodynamic instability, as well as the risks of sedation on PVR, including hypoxia and hypercapnic acidosis (due to hypoventilation and partial airway obstruction). Suctioning during flexible bronchoscopy may increase pulmonary arterial wedge pressure ($P_{paw}$) [35]. Although many chest physicians surveyed considered PH a contraindication to flexible bronchoscopy [36], it is performed in expert centres for suspected malignancy [37] to detect occult alveolar haemorrhage in pulmonary veno-occlusive disease (PVOD) with minimal sedation [38, 39], for avoidance of transbronchial biopsy and for screening for unstable or severely hypoxaemic patients. A recent retrospective study described minimal complications associated with bronchoalveolar lavage (BAL) or transbronchial biopsy with supplemental oxygen to maintain oxygen saturations greater than 90% (fractional concentration of oxygen in inspired gas 0.42 in PH patients *versus* 0.30 in controls; $p<0.01$) [40].

## Open-lung biopsy

PH increases complications following open lung biopsy [41]. Video-assisted thoracoscopic (VATS) lung biopsy, although less invasive, requires one-lung ventilation, and PH remains an independent risk factor for post-operative complications, including death [42]. This point is dramatically illustrated in a report where a diagnostic VATS biopsy was performed in a 43-year-old female with primary Sjögren's syndrome-associated PAH. Progressive PH crises followed the onset of one-lung ventilation, in association with severe intra- and post-operative bleeding. The PH was unresponsive to resumption of two-lung ventilation, and was complicated by progressive RV failure and death (fig. 2) [43]. Few lung biopsies are performed in patients with PH and, if necessary, an open procedure with a short ventilation pause may be preferable.

## Right heart catheterisation

Right heart catheterisation (RHC) in adults with PH (under local anaesthesia) is associated with a complication rate of 1%, mostly relating to venous access (*e.g.* pneumothorax), arrhythmias and hypotensive episodes. The overall mortality is 0.055% [44]. In children or adults requiring general anaesthesia (*e.g.* because of behavioural difficulties) the risk is appreciably higher. For example, in one report of RHC performed under general anaesthesia in 70 children with PH (including 23 with PAH), 6% suffered major complications requiring cardiac massage (including two dysrhythmias from catheter insertion), resulting in one death; although the sample size was small, all patients with major complications had severe PH on pre-catheterisation echocardiography [45]. In this context, what might be considered a relatively minor procedure in non-PH patients may be catastrophic in those with PH, especially when general anaesthesia is used.

# Non-cardiac surgery in patients with pre-existing PH

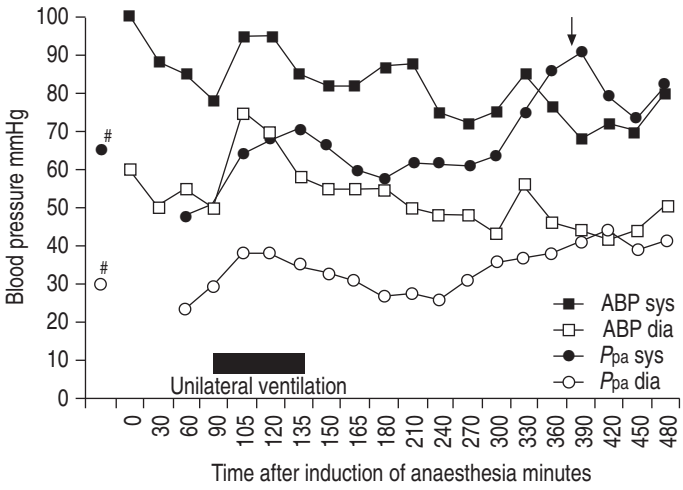


**Figure 2.** Changes in perioperative haemodynamics in the case described where pulmonary pressures increased immediately following deflation of the left lung for unilateral ventilation (black bar). This increase in pulmonary artery pressure ($P_{pa}$) was associated with the onset of pulmonary haemorrhage (arrow). Despite resuming bilateral ventilation and an emergency thoracotomy for intractable bleeding, the patient died of pulmonary hypertension and right ventricular failure post-operatively. ABP: arterial blood pressure; sys: systolic; dia: diastolic. #: pre-operative $P_{pa}$ values. Reproduced from [43] with permission from the publisher.

Studies of non-cardiac surgery including abdominal, gynaecological, orthopaedic and other procedures are categorised according to their emergency or elective nature, and according to operative risk: 1) low risk or minor surgery (includes endoscopic and superficial procedures); 2) intermediate risk; and 3) high risk or major surgery (includes procedures associated with major aortic/peripheral vascular surgery, laparotomy and major orthopaedic surgery) (table 3). Overall 28-day mortality ranges from 7% to 18% and morbidity from 14% to 42%, mostly due to RV failure, although other events including renal failure, sepsis and pneumonia can occur. Certain patient and procedural factors are associated with worse outcomes (tables 3 and 4).

Liver transplantation is becoming increasingly frequent, with patients having either acute or chronic indications. While acute liver failure

**Table 3.** Studies of perioperative morbidity and mortality in patients with pre-existing pulmonary hypertension (PH) undergoing general non-cardiac, non-obstetric surgery

| First author [ref.] | Study period | Type of PH/PAH# | PH severity | Procedure details¶ | Anaesthesia type | Major complications | Adverse events related to pre-operative PH severity? | Other associations |
|---|---|---|---|---|---|---|---|---|
| **Ramakrishna [46]** | 1991–2003 | 145 PH, including 45% PAH (20% IPAH), 19% lung disease, 8% CTEPH<br>Group 2 PH excluded | RHC RVSP 68±22 mmHg (n=68); mean $P_{pa}$ 44±15 mmHg (n=66); $P_{pcw}$ 15±8 mmHg (n=65); TTE RVSP 68±21 mmHg (n=145); 73% NHYA I–II, 27% III–IV) | Low and intermediate to high risk | All general, regional excluded | Mortality 10% (60% with respiratory failure, 50% with RV failure)<br>Morbidity 42% | Yes: baseline echo and ECG indices of worse RV function (for mortality but not morbidity)<br>Morbidity related to NYHA <II and 6MWD <330 m | Morbidity predictors (multivariate): history of pulmonary embolism, NYHA >II, intermediate- to high-risk surgery, duration of anaesthesia >3 hours<br>Other mortality predictors (univariate): anaesthesia without nitrous oxide, use of epinephrine and dopamine |
| **Minai [47]** | 1996–2002 | 28 procedures in 21 patients: 11 IPAH, 3 SSc, 2 POPH, 5 other | Mean $P_{pa}$ 53±14 mmHg: 38% NYHA II, 62% NYHA III–IV | Included 12 abdominal, 6 thoracic (including 3 VATS), 4 gynaecological and 4 orthopaedic | General (n=22)<br>Spinal (n=4)<br>Epidural (n=1)<br>Local (n=1) | Mortality 18%<br>Morbidity 14% | No data | No |
| **Carmosino [48]** | 1999–2004 | 156 children with PAH, median age 4 years: 88 IPAH, 33 CHD, 29 respiratory PH, 7 POPH | RHC baseline mean $P_{pa}$: 106 subsystemic (<70% systemic blood pressure); 30 systemic (70–100% blood pressure); 20 suprasystemic (>70% blood pressure) | 141 RHC and 31 CVP lines<br>Airway (n=28)<br>Abdominal (n=20)<br>Thoracic (n=8) | Sedation (n=49)<br>General volatile (n=148)<br>General total *i.v.* anaesthesia (n=45) | Mortality 1.3% overall<br>Morbidity (PH crises) in 3.8% overall | Yes: significantly more major complications if suprasystemic baseline PH (p=0.014) | All major complications (including 2 deaths) occurred during RHC under general anaesthesia<br>Multivariate predictor was baseline suprasystemic PH |
| **Lai [49]** | 1999–2004 | 62 PH: 18% PAH, 44% group 2 PH, 21% group 3 PH | All TTE: mean s$P_{pa}$ 79±9.4 mmHg (no RHC data) | 40 intermediate and 22 low risk procedures (no high risk) | General (n=36)<br>Neuraxial blocks (n=21) | Mortality 9.7%<br>Morbidity 24% | Yes: significant associations with pre-operative s$P_{pa}$ (no data on RV function or 6MWD) | Emergency surgery, higher risk surgery and coronary heart disease (all p<0.05) |
| **Price [50]** | 2000–2007 | 28 PAH and non-operable CTEPH | All RHC: mean $P_{pa}$ 43±12 mmHg; PVRI 11.1±5.7 Wood units·m$^2$; 75% NYHA I–II, 25% NYHA III | 57% major and 43% minor; 16 abdominal surgery, 8 orthopaedic, gynaecological and mastectomy | General (n=14)<br>Regional (n=14) | Mortality 7% (RV failure)<br>Morbidity 29% | Yes: suggested for exercise-related data (shorter 6MWD and NYHA III-IV were worse (trends: p=0.058; p=0.14)) but not for resting haemodynamic data | Perioperative complications associated with emergency surgery (p<0.001), major surgery (p<0.05), long operative time (p<0.05)<br>Use of general anaesthesia > regional anaesthesia (p=0.12) |

Data are presented as mean±SD, unless otherwise stated. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; CTEPH: chronic thromboembolic pulmonary hypertension; SSc: systemic scleroderma; POPH: portopulmonary hypertension; CHD: congenital heart disease; RHC: right heart catheterisation; RVSP: right ventricle systolic pressure; $P_{pa}$: pulmonary artery pressure; $P_{pcw}$: pulmonary capillary wedge pressure; TTE: transthoracic echocardiography; NYHA: New York Heart Association; s$P_{pa}$: systolic $P_{pa}$; PVRI: pulmonary vascular resistance index; VATS: video-assisted thoracic surgery; CVP: central venous pressure; RV: right ventricle; 6MWD: 6-minute walking distance. #: 18–45% of patients had PAH; ¶: categorised as low, intermediate and high risk.

**Table 4.** Perioperative factors increasing risk in pulmonary hypertension procedures

| |
|---|
| **Patient factors** |
| New York Heart Association >II [46, 50] |
| Lower 6-minute walking distance [46, 50] |
| High pre-operative pulmonary vascular resistance [45, 48, 51] |
| Less pulmonary vasoreactivity (cardiothoracic/transplant) [52] |
| Right ventricular dysfunction (echocardiography) [45, 46] |
| Underlying coronary artery disease [49] |
| **Operative factors** |
| Emergency surgery [46, 50] |
| Major surgery [46, 50] |
| Long operative time [46, 50] |
| Intra-operative hypoxaemia [46] |
| Vasopressor requirements [46] |
| Avoidance of general anaesthesia [50, 53, 54] |
| Use of nitrous oxide as an anaesthetic gas [46, 50] |

accounts for 16% of orthotopic liver transplantation [55], it does not usually involve PH. Chronic liver disease is associated with true PH (portopulmonary hypertension (POPH)) in approximately 4% of cases [56]. Overall, orthotopic liver transplantation mortality in patients with POPH is 36% and in proportion to the severity of pre-operative PH. An important study showed that in the setting of POPH, when the pre-transplant mean $P_{pa}$ was <35 mmHg all patients survived, when mean $P_{pa}$ was 35–50 mmHg mortality was 50%, and when mean $P_{pa}$ was >50 mmHg mortality was 100% [51]. Therefore, it seems sensible that POPH should be treated aggressively prior to liver surgery in order to achieve a mean $P_{pa}$ of <35 mmHg and PVR <250 dyn·s·cm$^{-5}$ to improve outcomes, although prospective studies are not yet available.

Pregnancy is extremely high risk for patients with PAH. The RV fails to cope with increasing oxygen demand and the increase in blood volume that occurs from the second trimester onwards. The time immediately following delivery is a particularly dangerous time as massive fluid shifts occur after uterine contraction and can precipitate RV failure. Large retrospective case series prior to 1998 document obstetric mortality in the region of 30% to 50% [57], and more recently as high as 25% [53]. However, a recent multicentre prospective study suggests mortality may be lower [56], especially in females with milder PH and responsiveness to calcium channel blockers (CCBs) [58]. In a study of mothers with PAH (New York Heart Association (NYHA) functional class) I–III prior to pregnancy), where overall mortality was 36%, caesarean section was associated with a 22% mortality [59]. The current practice in this high-risk patient group is to perform elective caesarean delivery at 32–34 weeks using regional or general anaesthesia. In addition, large bolus dosing of oxytocin (which may cause tachycardia and hypotension) is avoided.

## Selecting patients and predicting operative risk

Predicting operative risk of mortality or morbidity (principally relating to RV failure) is very difficult, and in PH is based mostly on small studies, thereby precluding multivariate analysis (table 3). Surgical factors increasing risk include emergency surgery, longer procedures and high-risk surgery (table 4). In addition, a number of patient factors have been identified. Higher levels of pre-operative PH [48, 49, 51] and RV dysfunction [45, 46] are especially adverse. Dynamic exercise testing (NYHA functional class and 6-minute walking distance (6WMD)) may provide additional prognostication [46, 50]. In the setting of cardiac surgery or transplantation, patients exhibiting less pre-operative pulmonary vascular reactivity (using 100% oxygen and 10–80 ppm NO) suffer more perioperative PH complications [52]. However, given than only 5–10% of patients with IPAH would be "acute vasoresponders" [60], this is unlikely to be such a useful test in all types of PH.

## Perioperative management

Multi-disciplinary planning for patients undergoing elective surgery is crucial, and more challenging for emergency procedures. Multi-disciplinary team members include those with the most experience among surgeons, anaesthetists and intensivists, as well as the PH team. Post-operative haemodynamic monitoring on a level 2 or higher ICU may be warranted for at least

48 hours, or longer in obstetric cases. The factors to consider in planning elective surgery are summarised in table 5, and anticipation and prevention of PH crises and RV failure is the key aim.

## Pre-operative anaesthetic assessment

Functional status is obtained from the patient's history, assessment of exercise tolerance and disease stability, as well as whether a recent change in therapy has occurred. Baseline haemodynamics should be recorded from the most recent RHC study, and an up-to-date ECG, brain natriuretic peptide (BNP) and echocardiogram (assessment of RV function) should be obtained. Exercise assessment is also important (NYHA class and 6MWD) given the functional limitation of the pulmonary circulation to cope with increased blood flow in PH. It is also likely that operative risk in PH is related to cardiopulmonary exercise test indices, as in major surgery in the non-PH population [62]. A review of medications is needed during liaison with the PH team, including a detailed plan for potential rapid use of *i.v.* or inhaled PH therapies. Understanding that the risk of surgical bleeding might be increased by the combination of post-operative heparin with the antiplatelet effects of prostacyclins is important, as is agreement among all team members of the risk stratification, the approach to the case, the plans in the event of a PH crisis, and the approach to post-operative haemodynamic monitoring.

## Perioperative monitoring

The choice of invasive pressure monitoring and/or of RV function is a balance among preference, familiarity and availability. At a minimum, central venous pressure (CVP) monitoring and

**Table 5.** Factors to consider when planning elective surgery in pulmonary hypertension (PH)

| |
|---|
| **Prevention of perioperative PH crises** |
| Maximise PH clinical status (ideally stable disease, good RV function) |
| Maximise PH treatment pre-operatively |
| Sensible, although no current studies support impact on perioperative outcomes |
| Optimise non-oral pulmonary vasodilator therapies |
| May require commencement and titration of intravenous therapy in the weeks prior to surgery |
| Haemodynamic monitoring |
| Intra-operatively: minimum of an arterial line, CVP±echocardiography (trans-oesophageal) and PAC |
| Post-operatively: where (HDU/ICU), how and for how long |
| Intra-operative management |
| Plan anaesthetic to minimise intra-operative surges in PVR (high $F_{i,O_2}$) and avoid general anaesthesia, if possible, acidosis and certain drugs (see table 1) |
| Maximise RV function: care with fluid loading and consider pre-emptive use of inotropes/vasopressors |
| **Planning for treatment of perioperative PH crises** |
| Emergency drugs to include: |
| Vasopressors (noradrenaline and vasopressin) |
| Inotropes (*e.g.* dobutamine and adrenaline) or inodilators (*e.g.* levosimendan and milrinone) |
| Pulmonary vasodilators (inhaled nitric oxide, inhaled/*i.v.* prostacyclin, inhaled iloprost, *etc.*) |
| **Planned cessation of warfarin (example of guideline)** |
| Stop warfarin at least 5 days prior to elective surgery |
| Bridge with therapeutic LMW or unfractionated heparin |
| Withhold LMW heparin for 24 hours (unfractionated heparin 4 hours) prior to surgery |
| **Postoperatively, if no operative bleeding, resume heparin 24 hours after minor or 48–72 hours after major surgery** |
| **Planning for regional anaesthesia[#]** |
| Neuraxial anaesthesia contraindicated in platelets $<$80,000 per mm$^3$ or INR $>$1.5 |
| Stop therapeutic heparin 24 hours prior to regional anaesthesia (12 hours for prophylactic dose) |
| Can restart heparin 2 hours after epidural catheter removal |

RV: right ventricle; CVP: central venous pressure; PAC: pulmonary arterial catheterisation; HDU: high-dependency unit; ICU: intensive care unit; PVR: pulmonary vascular resistance; $F_{i,O_2}$: inspiratory oxygen fraction; LMW: low molecular weight; INR: international normalised ratio. [#]: American Society of Regional Anaesthesia Guidelines, 2010 [61].

intra-arterial monitoring will reflect the onset of RV failure by increasing right atrial pressure ($P_{ra}$) in the setting of systemic hypotension. It could be argued, however, that waiting for the onset of RV failure is a late sign, and that the measurement of $P_{pa}$ and the calculation of PVR (also requiring cardiac output and $P_{pcw}$) from pulmonary arterial catheter measurements is important, with the $P_{paw}$ indicating the pre-/post-capillary cause of acute PH. However, the measurement of $P_{pa}$ should not be relied upon in isolation as it will fall in the context of a falling cardiac output. In addition, insertion of pulmonary arterial catheters is not without risk, and development of an intractable arrhythmia during insertion may precipitate a PH crisis. Noninvasive monitors (*e.g.* lithium dilution monitors, such as LiDCO (LiDCO Ltd, Cambridge, UK)) may be useful to monitor cardiac output post-operatively. Although not a continuous monitor as such, echocardiography is useful to assess RV function and PVR (an increasing PVR suggested by shortening of pulmonary acceleration time <80 milliseconds), but requires adequate views and an experienced second operator. It is extremely difficult to monitor the patient and administer anaesthesia if a single operator must also monitor the echocardiograph.

## Anaesthetic techniques

If practical, the choice between general and regional anaesthesia is important. General anaesthesia involves administration of gaseous or *i.v.* drugs to induce central neurological depression, and frequently involves endotracheal intubation and positive pressure ventilation. Regional anaesthesia consists of neuraxial anaesthesia (spinal, epidural and combined spinal epidural (CSE)), where drugs are administered in close proximity to the spinal cord and nerve roots, and peripheral nerve blocks, *e.g.* brachial plexus block for upper limb surgery. The comparative effects of regional and general anaesthesia are outline in table 6. Both general anaesthesia and neuraxial blocks have potential adverse pulmonary vascular and RV effects but these are probably less severe in carefully titrated continuous epidural anaesthesia. In addition, airway instrumentation may increase PVR and heart rate *via* sympathetic stimulation [15] and positive pressure may reduce RV preload. A marked drop in systemic vascular resistance (SVR) following a single dose of spinal anaesthesia may cause systemic hypotension, critically lower RV coronary perfusion and compromise RV function. In addition, a lowering of the SVR may worsen the right-to-left shunt in patients with Eisenmenger's syndrome. Acute reductions in SVR are less likely with low-dose spinal or CSE techniques. In a meta-analysis of almost 10,000 general patients without PH, the use of neuraxial blockade compared to general anaesthesia reduced post-operative all-cause mortality and morbidity [63], although this may simply relate to avoidance of general anaesthesia. This is also suggested by some (not all) PH clinical studies [50, 53, 64]. The consensus amongst anaesthetists is that regional anaesthesia may be preferable in PH, when surgery permits. Neuraxial blocks are, however, contraindicated in anticoagulated patients due to the risk of spinal haematoma, thus may not be practical for emergency procedures in PH patients. Finally, experimental and clinical reports suggest that blockade of cardiac sympathetic nerves during thoracic epidural anaesthesia in

**Table 6.** Comparison of key differences between regional and general anaesthesia

| | Regional | | General |
|---|---|---|---|
| | Single spinal dose[#] | Continuous epidural | |
| **Onset** | Rapid | Gradual | Titrated[¶] |
| **Impact on systemic vascular resistance** | +++ | Onset, dose | Onset, dose |
| **Airway manipulation** | | | ++ |
| **Ventilation** | Spontaneous | Spontaneous | Usually PPV |
| **Anticoagulation** | Spinal haemorrhage | Spinal haemorrhage | No risk |

PPV: positive pressure ventilation. [#]: a continuous spinal dose may bridge the effects between a single spinal dose and continuous epidural; [¶]: a rapid sequence induction is not titrated, but if this is not indicated, general anaesthesia can be induced gradually.

PH may limit the inotropic response of the acutely disturbed RV [65, 66], a consideration for thoracic epidural anaesthesia, which may be indicated for perioperative analgesia for a high laparotomy.

### Planning for PH crises

Avoiding precipitants of perioperative PH is ideal but these episodes may be unpredictable; thus, prompt recognition and aggressive treatment are crucial. Management strategies include: 1) maintenance of SVR to prevent RV ischaemia; 2) reducing PVR; and 3) improving RV/biventricular function. Several useful reviews have been published on this subject [67–69]. The principles are outlined below.

#### *Treatment of hypotension*

Hypotension in this setting is most likely to worsen severe RV failure and should be treated aggressively and concurrently with steps the steps listed below, *i.e.* without stopping pulmonary vasodilators. Fluid challenges should be cautious as $P_{ra}$ will be elevated. Vasopressors include noradrenaline (up to 0.5 μg per kg per min), which has been shown to improve coronary blood flow in several models of acute RV failure. Low-dose vasopressin may also be useful [70].

#### *Reducing PVR*

Selective inhaled pulmonary vasodilators have been used in many perioperative settings and, on the whole, are preferable to systemic non-selective vasodilators, which may inhibit appropriate hypoxic vasoconstriction, reduce SVR and hence, right coronary perfusion pressure. Despite this, *i.v.* sildenafil reduced PH and ICU length of stay in children with post-operative PH following cardiac surgery [71]. Inhaled pulmonary vasodilators including NO, inhaled prostacyclin and iloprost have been shown to reduce PVR in several perioperative settings including: heart transplantation surgery [72–74], following pulmonary endarterectomy [75], LV assist device-associated acute RV failure [76], and in patients with mitral stenosis undergoing mitral valve surgery [77]. Inhaled milrinone has been used to aide weaning from CPB [78]. Inhaled iloprost may even be more effective than inhaled NO in patients being weaned off CPB [79].

#### *Improving RV/biventricular function*

Once RV preload is adequate (may require cautious monitored fluid challenges or off-loading by diuresis), inotropic agents are useful. These include sympathomimetic agents, such as dobutamine, and inodilators including levosimendan (a calcium sensitiser) and milrinone (a phosphodiesterase type-3 inhibitor). In some centres, mechanical support using extracorporeal circulations and RV assist devices are options for reversible causes or as a bridge to transplantation.

## Conclusion

Patients with PH represent one of the highest risk patient groups presenting for surgery. Current mortality estimates are 7–18% for general surgery, 35% for liver transplantation (in moderately severe POPH) and 22% or higher for caesarean delivery. Retrospective single-centre studies have been small and the heterogeneity of various PH subtypes and surgical procedures makes prediction of risk for an individual patient difficult. This should be helped by larger prospective studies on the horizon. Current studies suggest that the risk of perioperative mortality and morbidity increases in those with more severe haemodynamic impairment, and importantly in those with pre-existing RV dysfunction. The acute adverse effects on RV physiology, even in patients with seemingly mild haemodynamic impairment undergoing minor diagnostic procedures, should not be under estimated; especially those related to general anaesthesia. A multidisciplinary approach to management is essential, with a predefined emergency plan for the management of PH crises and acute RV failure, and sufficient perioperative haemodynamic monitoring. Future research to guide

patient selection, predict operative risk and ascertain whether aggressive pre-operative treatment of poorly controlled PH may influence surgical outcomes is important.

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# Chapter 19

# New drugs for pulmonary hypertension

*Caroline O'Connell, Dermot S. O'Callaghan and Sean Gaine*

**SUMMARY: Pulmonary hypertension (PH) is a devastating disease for which effective therapies have only recently become available. Currently available treatments are based on three therapeutic pathways and drug classes: prostacyclin analogues, endothelin receptor antagonists (ERAs) and phosphodiesterase type-5 inhibitors (PDE-5 I). While the use of these drugs often confers improvements in important clinical parameters, the prognosis for most PH patients remains poor and more effective approaches are required. Potential novel therapeutic strategies include agents that demonstrate enhanced targeting of pathways that are the focus of existing treatments (*i.e.* prostacyclin, nitric oxide (NO) and endothelin pathways) and agents that act on entirely new targets. In this regard, the "Holy Grail" of drug development remains the identification of compounds that are capable of reversing the pathological remodelling that is characteristic of PH, thereby restoring normal pulmonary vascular structure and function. Looking beyond pharmacotherapy, research efforts examining the potential role of endothelial progenitor cells as a treatment alternative for PH are also underway. This chapter highlights agents at different stages of clinical development that may become part of the future PH therapeutic armamentarium.**

**KEYWORDS: Endothelial progenitor cell, endothelin antagonist, guanylate cyclase stimulator, prostacyclin receptor agonist, rho kinase, tyrosine kinase inhibitors**

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In pulmonary hypertension (PH), the mean pulmonary artery pressure ($P_{pa}$) is elevated (25 mmHg or greater), resulting in symptoms of dyspnoea, chest pain and dizziness. Without treatment, patients inevitably develop progressive and ultimately fatal right heart failure. However, remarkable advances have been made in the treatment of PH over the last decade, which is reflected in improved survival rates. Indeed, the French national registry recently reported 3-year survival in patients with idiopathic, familial or anorexigen-associated pulmonary arterial hypertension (PAH) of 58% [1]. This compares favourably with US figures from 1991 of 34% in a similar patient group, prior to the availability of currently licensed treatments [2]. While these therapies show favourable effects on patient symptoms, exercise capacity and pulmonary haemodynamics, a cure for PH remains elusive and there is a clear need for more effective

approaches. A large number of candidate drugs are currently at various stages of development and there is hope that, over the next decade, novel compounds with even greater efficacy will enter the clinical arena.

It is generally accepted that endothelial dysfunction plays an important role in the pathobiology of PAH. An imbalance between endothelium-derived vasodilators and vasoconstrictors leads to excessive pulmonary vasoconstriction, vascular proliferation and, ultimately, to vascular remodelling. Available PAH therapies aim to restore this imbalance (fig. 1) [3]. These comprise the prostanoid, phosphodiesterase type-5 inhibitor (PDE-5 I) and endothelin receptor antagonist (ERA) pharmacological classes that target the prostacyclin, nitric oxide (NO) and endothelin pathways, respectively. Much of the focus of new drug development is the identification of agents that have similar mechanisms of action to currently available drugs but show greater efficacy and tolerability. Despite agents from these three classes having definite vasodilator, anti-inflammatory, antiplatelet and antiproliferative effects, they demonstrate little, if any, capacity to reverse pathological remodelling. Therefore, new pharmacological approaches targeting the prostacyclin, NO and endothelin pathways with enhanced antiproliferative activity are being sought. Moreover, a host of agents that focus on other relevant molecular targets are being targeted.

## Exploring current pathways

### The endothelin pathway

Endothelin (ET)-1 is a potent vasoconstrictor and smooth muscle mitogen that is overexpressed in the plasma and lungs of patients with PAH [4]. The development of the ERA therapeutic family, comprising bosentan (a nonselective $ET_A$ and $ET_B$ receptor antagonist) and ambrisentan (a selective $ET_A$ antagonist), was an important milestone in the history of PH pharmacotherapy. These treatments confer clinical improvements, are easy to administer (orally active) and are generally well tolerated. However, there is considerable interest in the identification of agents that act on this pathway that have greater potency, coupled with reduced potential for side-effects, such as hepatic injury and teratogenicity [5].

Macitentan is an orally active ERA that has a higher affinity for lipophilic membranes than bosentan, resulting in enhanced tissue penetration. Because of prolonged local tissue activity, single daily dosing is possible. Macitentan does not interfere with normal bile acid secretion, therefore reducing the risk of hepatotoxicity. Preliminary study data indicate macitentan is generally well tolerated (headache being the most commonly reported adverse effect) and demonstrates dose-dependent pharmacokinetics [6–8]. A phase III, multicentre, double-blind, placebo-controlled, event-driven trial of the effect of macitentan on morbidity and mortality in approximately 700 PAH patients is underway [9].

### The prostacyclin pathway

Endothelium-derived prostaglandin $(PG)I_2$, or prostacyclin, is a potent pulmonary vasodilator that also exerts antithrombotic, antiproliferative, antimitogenic and immunomodulatory activity. The pulmonary vasculature and serum of PAH patients are characterised by reduced expression of prostacyclin synthase and prostacyclin metabolites [10]. Several synthetic prostacyclin analogues, also termed prostanoids, which mimic the effects of endogenous prostacyclin have been developed over the last 20 years. Epoprostenol has a very short half-life (approximately 5 minutes) that necessitates its continuous infusion *via* an indwelling central venous catheter with the attendant potentially fatal risks of catheter-related bloodstream infections and catheter dislodgement [11]. Other licensed prostanoids include treprostinil, which can be administered by intravenous, subcutaneous or inhaled routes, and iloprost, which is available in *i.v.* and inhaled formulations [12].

Administration of epoprostenol is cumbersome, necessitating a storage cassette surrounded by frozen gel packs that must be changed daily. Recently, a formulation of epoprostenol that remains

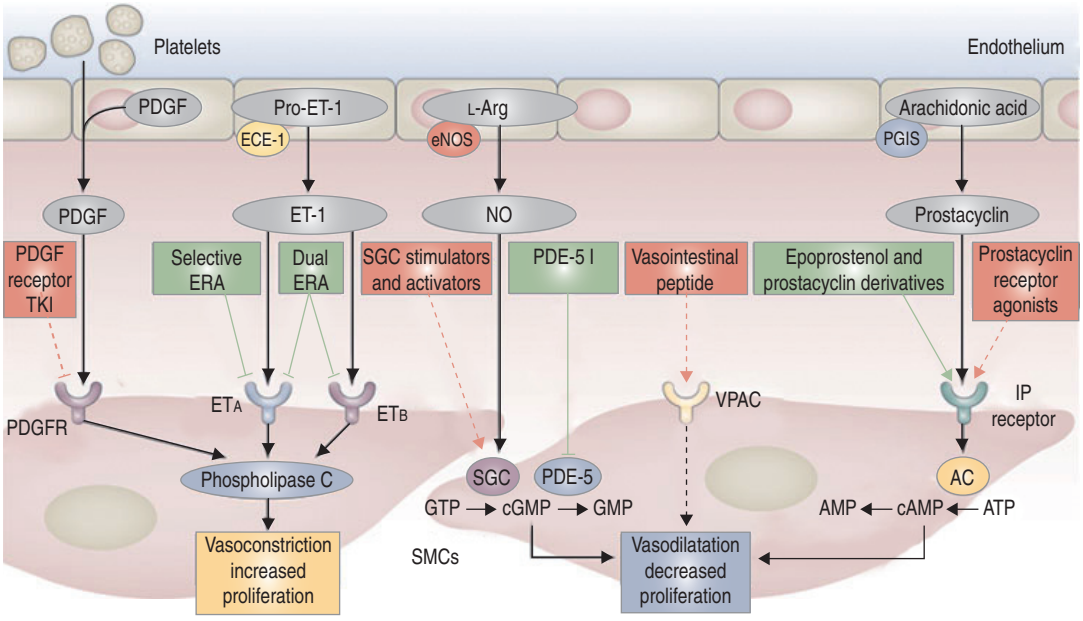


**Figure 1.** Current and emerging targets and therapies for pulmonary hypertension (PH). Pulmonary artery smooth muscle cell (SMC) therapeutic targets and corresponding licensed (green boxes) and investigational (red boxes) treatment approaches for pulmonary arterial hypertension (PAH). Arrows represent receptor stimulation, whereas terminated lines represent receptor blockade. PDGF: platelet-derived growth factor; PDGFR: platelet-derived growth factor receptor; TKI: tyrosine kinase inhibitor; ET-1: endothelin-1; ECE: endothelin-converting enzyme; ERA: endothelin receptor antagonist; $ET_A$ and $ET_B$: endothelin receptors; Arg: arginine; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; sGC: soluble guanylate cyclase; GTP: guanidine triphosphate; cGMP: cyclic guanidine monophosphate; GMP: guanidine monophosphate; PDE-5 I: phosphodiesterase type-5 inhibitor; PDE-5: phosphodiesterase type 5; VPAC: vasointestinal peptide receptor; PGIS: prostacyclin I synthase; AC: adenylate cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; AMP: adenosine monophosphate. Reproduced and modified from [3] with permission from the publisher.

stable at room temperature for at least 24 hours has been developed. Accordingly, cassettes need only be changed by patients every second day [13]. An open-label, single-arm safety, efficacy and quality of life study of 20 PAH patients using this novel formulation is underway [14].

Parenteral prostanoids are important treatment options for PAH patients, particularly those with advanced disease. However, the associated delivery systems required for the administration of these agents are a major drawback. An effective orally active prostanoid is therefore highly desirable, although currently, the only country in which an oral prostanoid is licensed for use is Japan, which granted regulatory approval for beraprost. The effects of adding oral treprostinil to a PDE-5 I and/or an ERA was examined in 354 PAH patients in the phase III FREEDOM-C trial [15]. The primary end-point of change in 6-minute walking distance (6MWD) was not reached, though a large patient dropout rate because of prostanoid-related side-effects was observed. The FREEDOM-C2 was similar in design to its predecessor but assessed the efficacy of oral treprostinil using smaller incremental doses of study drug [16]. This trial also failed to reach its primary end-point: patients receiving study drug demonstrating a placebo-adjusted change in median 6MWD of only 10 m ($p=0.089$) [17]. However, a third phase III trial (FREEDOM-M), in which the efficacy of oral treprostinil as monotherapy in 349 PAH patients was examined, was positive, with the patients who were randomised to active drug demonstrating a placebo-adjusted improvement in 6MWD of 23 m ($p=0.0125$) at 12 weeks [18]. A phase III, randomised, double-blind, placebo-controlled, event-driven study to examine the effect of addition of oral treprostinil to maintenance PDE-5 I and/or ERA therapy on time to clinical worsening is expected to commence enrolement in 2012. A new slow-release formulation of beraprost is also currently under investigation, as consistent long-term benefits have not been demonstrated with the original drug.

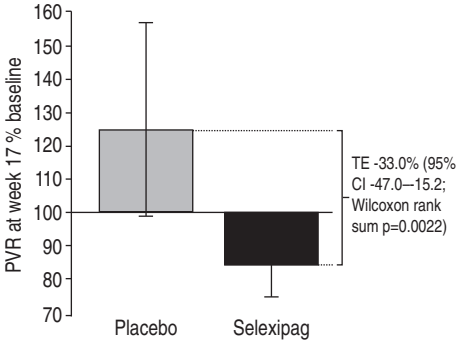


**Figure 2.** Change in pulmonary vascular resistance (PVR) following treatment with selexipag. Baseline mean ± SD PVR for the treated population (n=32) was 948.6 ± 428.0 dyn·s·cm$^{-5}$ and for the placebo group (n=10) was 867.2 ± 379.38 dyn·s·cm$^{-5}$. Data are presented as geometric mean (95% confidence interval (CI)). TE: treatment effect. Reproduced and modified from [23] with permission from the publisher.

Inhaled treprostinil is not licenced in Europe. Nevertheless, a metered-dose inhaler (MDI) formulation has been developed, which has the advantage of easier administration compared with the nebulised preparation. In a study of 39 PAH and chronic thromboembolic PH (CTEPH) patients, acute administration of different doses of inhaled treprostinil *via* MDI led to significant reductions in both mean $P_{pa}$ and pulmonary vascular resistance (PVR). Pulmonary selectivity was also confirmed, with patients experiencing no systemic adverse effects at high doses, unlike inhaled iloprost [19]. A long-term randomised controlled trial to evaluate the efficacy and safety of treprostinil delivered by MDI now appears justified.

### *Selexipag*

The prostacyclin I receptor (PIR) is found on blood vessels, leukocytes and platelets, and, when activated, leads to vascular smooth muscle relaxation and vasodilatation through downstream increased adenylate cyclase activity and upregulation of cyclic adenosine monophosphate (cAMP) levels. Selexipag is an oral PIR agonist that represents the first agent from a new pharmacological class that may be beneficial in PAH. The drug has the theoretical advantage of low affinity for PGE receptor 3, which, when activated, predominantly exerts vasoconstrictor activity [20]. Because the pro-drug undergoes initial hepatic metabolism following ingestion, patients experience fewer gastrointestinal side-effects compared with those treated by prostanoids. In a phase I study of five healthy male Caucasian volunteers, headache was the most commonly reported adverse event [21]. In addition, a half-life of 7.9 hours allows for twice daily dosing. A proof-of-concept, phase II multicentre study of 43 PAH patients showed that 17 weeks of selexipag treatment was well tolerated and led to a 30.3% reduction in mean PVR ($p<0.0045$) [22, 23]. Modest improvements in 6MWD and brain natriuretic peptide (BNP) levels were also observed with selexipag treatment, though the study was not powered to test for changes in these parameters (fig. 2). The phase III, multicentre, double-blind, placebo-controlled GRIPHON ($PGI_2$ Receptor Agonist in Pulmonary Arterial Hypertension) trial is underway to assess efficacy and safety of selexipag in 670 group 1 PAH patients, with time to clinical worsening established as the primary efficacy end-point [24].

## The NO pathway

Modulation of pulmonary vascular tone is in part mediated by NO through its action on the second messenger cyclic guanosine monophosphate (cGMP) *via* soluble guanylate cyclase (sGC). Documented favourable effects of cGMP in the pulmonary vasculature include smooth muscle relaxation, inhibition of smooth muscle cell proliferation and platelet aggregation, and potential reversal of remodelling *via* activation of pro-apoptotic pathways [25]. The breakdown of cGMP is inhibited by the PDE-5 I class of agent, of which sildenafil and tadalafil have emerged as effective treatments that favourably modulate important outcome measures, including exercise capacity, pulmonary haemodynamics and clinical worsening [26, 27].

Vardenafil is another PDE-5 I licensed for erectile dysfunction that is also under investigation in PAH [28]. An open-label study examining the effect of vardenafil on 45 patients with idiopathic, connective tissue disease (CTD)-associated and congenital heart disease-associated PAH revealed improvements in haemodynamics, 6MWD and functional class after 1 year of treatment [29]. Recently, favourable effects on exercise capacity and pulmonary haemodynamics were reported in

a randomised, double-blind, placebo-controlled study of 66 Chinese patients with PAH randomised to vardenafil (5 mg once daily for 4 weeks then 5 mg twice daily; n=44) or placebo (n=22) for 12 weeks [30].

### *Riociguat*

Production of cGMP is dependent on endogenous NO levels. However, patients with PAH typically have low NO levels, thus limiting the efficacy of PDE-5 I agents [31]. Inhaled NO has demonstrated efficacy in PAH, but its short half-life and requirement for cumbersome delivery systems preclude use as an outpatient therapy. Riociguat is a new oral agent that stimulates sGC and increases its sensitivity to NO, resulting in increased cGMP levels and a half-life of 10–12 hours (fig. 3) [32]. This mechanism of action leads to vasodilatation and inhibition of smooth muscle cell proliferation and platelet aggregation. Moreover, in contrast to PDE-5 I, riociguat not only increases the sensitivity of sGC to NO but also mediates its effects independent of NO levels.

A proof-of-concept, acute haemodynamic study showed that riociguat reduced PVR and improved cardiac output in patients with moderate-to-severe PH of different aetiologies (PAH, distal CTEPH and patients with PH-associated interstitial lung disease) when compared with inhaled NO [32]. A phase II, multicentre, open-label study of patients with functional class II–III PAH (33 patients) or CTEPH (44 patients) showed reduced PVR (-215 dyn·s·cm$^{-5}$ from baseline, $p<0.0001$), and improved 6MWD (55 m, $p<0.0001$) and N-terminal (NT)-proBNP levels after 12 weeks of riociguat [33]. Riociguat tends to reduce systolic blood pressure; however, this effect seems to abate with longer-term administration and overall treatment is relatively well tolerated, with dyspepsia, headache, nasal congestion and hypotension the commonest adverse effects. The randomised, multicentre, placebo-controlled Pulmonary Arterial Hypertension sGC-Stimulator Trial (PATENT) is due to enrol 462 patients and will examine change in 6MWD as the primary end-point [34]. Borg score, functional class, BNP levels, pulmonary haemodynamics, quality of life and time to clinical worsening will be examined as secondary end-points.

As yet, no drug has been approved for the treatment of CTEPH in patients with persistent PH post-thromboendartectomy (PTE) surgery or who are deemed unsuitable candidates for this intervention. However, preliminary data suggest that riociguat may be efficacious in these patients. The Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial (CHEST)-1 is a multicentre study in which 270 patients with CTEPH assessed as either inoperable or persistent PTE will be randomised to riociguat or placebo for 16 weeks to determine whether treatment improves exercise capacity [35]. A 5-year extension study is also planned. Although riociguat may have a synergistic effect with PDE-5 I, systemic hypotension may limit the clinical use of this combination [36]. PATENT-PLUS, a phase II trial of sildenafil and riociguat using the change in supine systolic pressure from baseline as the primary efficacy end-point, should help better evaluate this strategy [37].

## Exploring new pathways

### Tyrosine kinase

Dysregulated proliferation of endothelial and smooth muscle cells leads to vascular remodelling and increased PVR in PAH. Because of their activity on mitogenic growth factor receptors, tyrosine kinase inhibitors (TKIs) have thus attracted much interest as a potential PH therapeutic option.

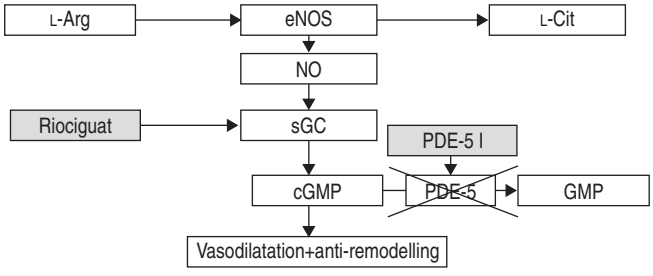


**Figure 3.** Mechanism of action of riociguat. Arg: arginine; eNOS: endothelial nitric oxide synthase; Cit: citrulline; NO: nitric oxide; sGC: soluble guanylate cyclase; cGMP: cyclic guanidine monophosphate; PDE-5: phosphodiesterase type 5; PDE-5 I: PDE-5 inhibitor; GMP: guanidine monophosphate.

### *Imatinib*

Platelet-derived growth factor (PDGF) is a potent endothelial and smooth muscle mitogen that contributes to abnormal pulmonary vascular remodelling [38]. PDGF receptor expression is increased in the lungs of PH patients compared with controls, and blockade of this target may be beneficial in PH [39]. Imatinib, an oral TKI that binds to the tyrosine kinase domain on the PDGF receptor, has been evaluated as a potential PH treatment. In a phase II, 24-week study of 59 PAH patients with persistent functional class II–IV symptoms despite standard therapy, imatinib failed to significantly improve 6MWD but appeared to have a favourable effect on pulmonary haemodynamics [40]. Treatment was generally well tolerated, with nausea, headache and peripheral oedema being the most commonly reported problems. Interestingly, patients with the most severe haemodynamic impairment appeared to derive greatest benefit from therapy; this observation influenced the design of the phase III IMPRES (Imatinib in Pulmonary Arterial Hypertension, a Randomized Efficacy Study) trial [41]. This placebo-controlled study enrolled 202 patients with severe disease (PVR over 12.5 Wood units) already receiving at least two PAH therapies. After 24 weeks, imatinib-treated patients had placebo-corrected improvements in 6MWD (+32 m, $p=0.002$), PVR (-379 dyn·s·cm$^{-5}$, $p<0.001$) and cardiac output (+0.88 L·min$^{-1}$, $p<0.001$).

Although TKIs may prove to be efficacious in PAH, significant concerns have been raised regarding potential toxicity with this class of drug. In particular, cardiotoxicity and an increased incidence of subdural haematomata are of greatest concern. Imatinib is also an inhibitor of the cytochrome (CY)P450 3A4 enzyme system inhibitor, which may potentially cause clinically important interactions with warfarin, sildenafil and bosentan.

### *Other TKIs*

Among the other TKIs being evaluated as potential PH therapies, nilotinib has a better safety profile than imatinib despite its associated risk of QT prolongation and sudden cardiac death [42]. A multicentre, phase II study of nilotinib in PAH is underway to test the effect of three doses of nilotinib *versus* placebo with change in PVR selected as the primary end-point [43]. Sorafenib is a less specific multi-kinase inhibitor that inhibits not only PDGF, vascular endothelial growth factor (VEGF) and c-Kit, but also targets the Raf/ MEK/extracellular signal-regulated kinase (ERK) pathway. In rat studies, sorafenib treatment attenuated pulmonary vascular remodelling and improved pulmonary haemodynamics [44]. A phase I, open-label study of 12 PAH patients previously treated with prostanoids and/or sildenafil confirmed that the addition of sorafenib for 16 weeks was well tolerated [45]. The most frequent adverse effects were diarrhoea, hand–foot syndrome, rash and alopecia. Although patients showed improvements in exercise capacity, only a small decline in median cardiac index was reported. Further underscoring the need for careful evaluation of the potential deleterious effects of this therapeutic class is the recent report of cases of reversible PH associated with treatment by dasatinib, a Bcr-Abl and c-Kit tyrosine kinase inhibitor used in the treatment of chronic myeloid leukaemia [46, 47].

## Pathways not delivering on early expectations

### Serotonin

Serotonin induces vasoconstriction, smooth muscle proliferation and platelet aggregation [48]. Furthermore, serotonin levels and expression of its associated 5-HT$_{2B}$ receptor are known to be increased in idiopathic PAH (IPAH) [49, 50]. The serotonin transporter is a potential therapeutic target as certain alleles of the transporter have been linked to an increased risk of developing PH [51, 52]. The selective serotonin receptor inhibitor (SSRI) fluoxetine is a serotonin transporter inhibitor that protects against monocrotaline-induced smooth muscle proliferation in animal models [53]. Registry data from the USA have shown a reduced incidence of PH and better survival in PH patients treated with SSRIs [54].

Terguride is a type 2 serotonin receptor antagonist and partial dopamine agonist previously used for treatment of hyperprolactinaemia. Pre-clinical studies have shown that terguride has anti-inflammatory, antiproliferative and antifibrotic effects, and inhibits the development and progression of PH in monocrotaline-treated rats [55]. However, a multicentre, randomised, placebo-controlled, phase II trial evaluating the safety and effect of terguride on PVR at 12 weeks in 84 PAH patients in functional class II–IV has not proved fruitful. It remains to be determined whether targeting serotonin can provide a viable therapeutic option in the future.

### Vasoactive intestinal peptide

Vasoactive intestinal peptide (VIP) is a neurotransmitter hormone with vasodilatory, antiproliferative and anti-inflammatory effects. It binds to $VPAC_1$ and $VPAC_2$ receptors, and increases intracellular cAMP and cGMP, leading to vasodilatation. Experimental evidence also indicates that VIP regulates a number of genes involved in vascular remodelling [56]. VIP-depleted mice develop pulmonary vascular remodelling and PH, and these changes are attenuated when VIP is replaced [57]. In PH patients, VIP levels are reduced and VIP receptor expression is upregulated [57]. Aviptadil is a synthetic analogue of VIP that can be given parenterally or by inhalation. In a 24-week pilot study of eight treatment-naïve patients, treatment with inhaled VIP improved pulmonary haemodynamics (increase in cardiac index of 0.8 $L \cdot min^{-1} \cdot m^{-2}$ ($p<0.05$), and reduction in mean $P_{pa}$ of 10 mmHg ($p<0.01$), 6MWD (from 296 m to 409 m at 3 months) and dyspnoea levels) [58]. However, a subsequent phase II study comparing the effect of the addition of inhaled aviptadil to ERA and/PDE-5 I in 56 PH patients failed to meet its primary end-point of reduction in PVR [59]. Furthermore, there was no change observed in 6MWD, BNP levels or functional class after 12 weeks.

### Simvastatin

Statins reduce vascular cell proliferation and exhibit anti-inflammatory, antioxidant and antithrombotic effects. These agents block synthesis of mevalonate and isoprenoids (necessary for activation of the RhoA–Rho kinase pathway), and confer beneficial effects in animal models [60, 61]. In an open-label study of 16 PH patients treated with simvastatin in addition to standard PH therapy, there were improvements at 3 months in right ventricular (RV) systolic pressures and 6MWD [62]. However, two larger trials of statins in PAH have failed to reach their primary efficacy end-points, suggesting this class of drug may not be useful in PH [63, 64].

### Cicletanine

Cicletanine is an oral systemic antihypertensive that has effects on multiple molecular pathways including increased vascular NO production through stimulation of endothelial NO synthase (eNOS), increased prostacyclin synthesis, PDE-1 and -5 inhibition, scavenging of endothelial-derived superoxide, calcium channel blockade and diuresis. Improved haemodynamics were previously found in a small number of chronic obstructive pulmonary disease (COPD) patients with PH who were treated with cicletanine [65]. This lead to the launch of a phase II, randomised, double-blind, placebo-controlled, multicentre, dose-ranging trial of 160 PAH patients using change in 6MWD at 12 weeks as the primary end-point [66]. However, this trial was not completed.

## Pathways requiring further evaluation in patients

### Rho kinase pathway

Rho kinase is an enzyme that leads to smooth muscle contraction by increasing calcium ion sensitivity *via* its activity on myosin phosphatase. Increased levels of Rho kinase have been found in the lungs, smooth muscle cells and platelets of PAH patients [67]. The use of Rho kinase

inhibitors in animal models of PH have been shown to reduce smooth muscle cell contraction and proliferation, modulate endothelial dysfunction, impede migration of inflammatory cells and improve survival [68, 69]. Fasudil is a selective Rho kinase inhibitor administered by either *i.v.* or nebulised routes that has potential as a PH treatment. Though data regarding its use in humans are limited, administration of fasudil by the *i.v.* route led to an acute reduction of PVR by 20% in eight patients with severe PAH [70]. Inhaled fasudil also has favourable acute effects on the pulmonary vasculature in PAH patients and appears to show greater pulmonary selectivity than when given by the parenteral route [71, 72]. However, there are currently no data regarding longer-term effects of this agent [73]. Azaindole-1 is a highly selective oral Rho kinase inhibitor that improvess haemodynamics and reduces RV hypertrophy and pulmonary vascular remodelling in animal models [74, 75]. This drug has yet to be tested in humans.

### Adrenomedullin

Adrenomedullin is a peptide expressed in the lungs that possesses vasodilatory, anti-inflammatory and antioxidant activity. It has been shown to exert a regulatory role in pulmonary vascular homeostasis through its effects on the cAMP, NO and phosphatidylinositol 3-kinase pathways. Plasma levels of this peptide increase as PH worsens [76]. Inhaled adrenomedullin reduced PVR acutely and increased peak oxygen consumption during exercise in 11 patients with IPAH [77]. However, no longer-term data demonstrating sustained beneficial effects in patients are available.

### Dichloroacetate

Dichloroacetate is an inhibitor of the mitochondrial enzyme pyruvate dehydrogenase kinase that facilitates a switch from antiapoptotic glycolytic metabolism towards pro-apoptotic oxidative phosphorylation metabolism. This characteristic may promote regression of established vascular remodelling and in animal models of PH, dichloroacetate treatment caused reduction in PVR and RV hypertrophy, and improved survival [78, 79]. The first human dose-ranging phase I study in PAH is underway to assess the safety and tolerability of the addition of dichloroacetate to standard therapy in advanced disease [80].

### Other potential targets

There are a number of new pathways recently identified in PH that may translate into effective therapeutic targets in the future. Angiopoietin, for example, is a growth factor responsible for blood vessel maturation and maintenance, which could be another target for reversing vascular remodelling [81]. Furthermore, XNT, an angiotensin-converting enzyme 2 activator found in animals to attenuate RV hypertrophy and reduce RV pressure, could be investigated [82]. Indeed, agents already in use for other indications, such as carbonic anhydrase inhibitors (*e.g.* topiramate), may show some promise in the future for PH [74].

## Exploring stem cell pathways

Cell-based gene therapy, in which healthy bone marrow-derived endothelial cells are introduced into the pulmonary vasculature as a means of promoting healing and restoration of vascular homeostasis, is an intriguing treatment option for PH. Reversal of vascular remodelling and improved survival was found in animal models when endothelial progenitor cells (EPCs) were transfected with the eNOS gene and engrafted to distal pulmonary arterioles [83]. Further study indicates that dysregulated haematopoiesis may lead to the development of PAH, highlighting the potential importance of targeting this cellular population as a therapeutic target [84, 85]. A Chinese study found a 48-m improvement in 6MWD and 17% reduction in PVR in patients with IPAH at 12 weeks using stem cell-based therapy [86]. The PHACeT (Pulmonary Hypertension: Assessment of Cell Therapy) trial is currently underway in Canada, and is looking at the safety of EPC gene transfer of eNOS in 18 PAH patients with advanced disease [87].

**Table 1.** Key phase II and III clinical trials of investigative pulmonary arterial hypertension (PAH) therapies since the 2009 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines

| | Phase | Agent | Therapeutic class | Administration route | Primary study end-point | Study result |
|---|---|---|---|---|---|---|
| **Prostacyclin pathway** | | | | | | |
| TRIUMPH-1 | III | Treprostinil | Prostanoid | Inhaled | 6MWT | +20 m ($p<0.001$) at 12 weeks |
| FREEDOM-C | III | Treprostinil | Prostanoid | Oral | 6MWT | Negative study[¶] |
| NIPPON | II | Selexipag | Prostacyclin receptor agonist | Oral | Pulmonary haemodynamics | 30% decreased PVR ($p<0.01$) |
| GRIPHON | III | Selexipag | Prostacyclin receptor agonist | Oral | Time to clinical worsening | Study ongoing |
| **Endothelin pathway** | | | | | | |
| SERAPHIN | III | Macitentan | Tissue-targeting ERA | Oral | Time to clinical worsening | Study ongoing |
| **NO pathway** | | | | | | |
| PATENT-1 | III | Riociguat | sGC stimulator | Oral | 6MWT | Study ongoing |
| **VIP** | | | | | | |
| VIP | II | Aviptadil | VIP pathway | Inhaled | Pulmonary haemodynamics | Negative study[+] |
| **TKI** | | | | | | |
| IMPRES | III | Imatinib | TKI | Oral | Time to clinical worsening | Study ongoing |
| **Rho kinase pathway** | | | | | | |
| SiPHT | I and II | Simvastatin | HMG-CoA reductase inhibitor | Oral | RV mass (by MRI) | Negative study[§] |
| ASA-STAT | III | Simvastatin[#] | HMG-CoA reductase inhibitor | Oral | 6MWT | Negative study[ƒ] |

TRIUMPH: Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension; GRIPHON: $PGI_2$ Receptor Agonist in Pulmonary Arterial Hypertension; NO: nitric oxide; SERAPHIN: Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; PATENT: The Pulmonary Arterial Hypertension sGC-Stimulator Trial; VIP: vasoactive intestinal peptide; IMPRES: Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study; SiPHT: Simvastatin as a Treatment for Pulmonary Hypertension Trial; ASA-STAT: A Clinical Trial of Aspirin and Simvastatin for Pulmonary Arterial Hypertension; 6MWT: 6-minute walk test; PVR: pulmonary vascular resistance; ERA: endothelin receptor antagonist; sGC: soluble guanylate cyclase; TKI: tyrosine kinase inhibitor; HMG-CoA: hydroxyl-3-methyl-glutaryl coenzyme A; RV: right ventricular; MRI: magnetic resonance imaging. [#]: second arm of the study examining aspirin *versus* placebo was also negative using the same end-point. [¶]: placebo-corrected median change in 6MWT distance at week 16 of 11 m ($p=0.072$). [+]: no reduction in PVR compared with placebo, either after a single inhalation or after 12 weeks of treatment; no changes in 6MWT, N-terminal pro-brain natriuretic peptide levels or functional class after 12 weeks. [§]: reduced RV mass at 6 months but changes not sustained at 12 months. [ƒ]: trend toward worse 6MWT and dyspnoea at 6 months but study stopped early owing to futility in reaching primary end-point. Reproduced and modified from [3] with permission from the publisher.

## Combining pathways

The notion that a unifying molecular mechanism might be critical to the development of PAH seems improbable, given that there are numerous distinct clinical syndromes, environmental factors and genetic abnormalities that predispose to the disorder [88]. Experience has shown that using treatments that act on a single pathway are rarely consistently successful and there is at least a theoretic advantage to combining treatments that act on different molecular targets or different elements of the same target [89]. The most recent European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guidelines recommend dual combinations of any of the three available drug classes in patients without an adequate clinical response to monotherapy [90]. However, further clarification is required regarding whether upfront or sequential combination therapy is more beneficial, which of the various drug combinations is optimal, and the impact of potential drug–drug interactions. It is important to emphasise that clinical trials of combination treatment have, in general, found smaller improvements in 6MWD than might have been expected. This observation raises questions as to what the most appropriate trial end-points should be and whether future studies should focus more on event-free survival (time to hospitalisation, clinical worsening, addition of prostanoid, transplantation and death) [91]. AMBITION is a large randomised controlled trial of PAH patients assessing the effect of starting first-line combination therapy with ambrisentan and tadalafil *versus* ambrisentan or tadalafil alone [92]. The design of this trial is unique as the effect of first-line combination therapy, as opposed to sequential addition of therapy, will be examined. The study is expected to complete enrolment in 2013.

## Conclusion

The past 10 years have brought major advances to the treatment of PH. The increased choice of medications with easier modes of administration and fewer side-effects is welcome in the PH therapeutic arena, and many candidate drugs have shown promise in animal models and early human studies. However, rigorous evaluation of these potential agents in randomised controlled trials is mandatory in order to establish the risk/benefit profile (table 1) [14].

In the future, it is likely that most PH patients will be treated with at least one, if not several, therapeutic agents. This will affect the way novel drugs are tested in clinical studies over the coming decade, as they are likely to be studied in combination with these other agents. In the past, the dismal prognosis of PH meant that short-term end-points could be employed in order to secure regulatory approval for new drugs. With the ever-increasing number of available therapies, however, longer-term trials with harder end-points (*e.g.* event-free survival instead of short-term effects on exercise capacity) will be required [91]. In time, we may find that some of these new drugs and their combinations are more effective on certain types of PH than others. The optimal combination of strategies and potential interactions will need to be further defined.

### *Statement of Interest*

D.S. O'Callaghan's has current or previous relationships with the following pharmaceutical companies: AstraZeneca, Boehringer Ingelheim, GSK, Lilly, Novartis, Nycomed and Pfizer. S. Gaine has served on advisory boards, steering committees and drug safety boards for a number of pharmaceutical companies with an interest in pulmonary hypertension. Furthermore, he has received honoraria for speaking for companies including Actelion, GSK, Lily, Pfizer and United Therapeutics.

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# Chapter 20

# Lung transplantation for pulmonary hypertension

*Jens Gottlieb*[*] *and Paul A. Corris*[#,¶]

**SUMMARY: Lung transplantation (LTx) now offers an effective therapy for patients with end-stage pulmonary vascular disease. Debate continues as to which transplant operation should be performed for such patients. The major practical problem facing LTx at this time is a shortfall in suitable donor organs compared with the number of potential recipients. The shortfall in donor organs has led to the successful introduction of lungs from non-heartbeating donors. In the early post-operative period, primary graft dysfunction remains a major problem and, in the long term, chronic lung allograft dysfunction and infections are the leading causes of death. Extracorporeal membrane oxygenation (ECMO) may improve the perioperative management of pulmonary arterial hypertension (PAH) patients following LTx.**

**Patients who have received lung transplants and remain free of chronic lung allograft dysfunction enjoy an excellent standard of life, with normal or near-normal restoration of activities and good prospects for prolonged survival.**

**KEYWORDS: Extracorporeal membrane oxygenation, lung transplantation, primary graft dysfunction, pulmonary hypertension, selection criteria**

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Lung transplantation (LTx) is an established therapy option for patients with various end-stage lung diseases. Presently, the worldwide procedural frequency is approximately 3,200 transplants per year [1]. Unfortunately, the shortage of donor organs leads to every sixth patient on the waiting list of the Eurotransplant (www.eurotransplant.org) and United Network of Organ Sharing (UNOS; www.unos.org) registries dying before a donor organ is available. The most frequent underlying clinical indications are emphysema, lung fibrosis and cystic fibrosis (CF), although patients with pulmonary hypertension (PH) refractory to medical therapy also constitute a significant indication. In experienced centres, candidates for transplantation are chosen according to disease-specific factors after excluding contraindications.

PH is a haemodynamic and pathophysiological state that can be found in multiple clinical conditions. These have been classified into six clinical groups with specific characteristics [2]. Idiopathic pulmonary artery hypertension (IPAH; group 1) represents the condition with the most extensive availability of specific treatment options. Experience with LTx is mainly based on patients with pulmonary arterial hypertension (PAH). The other four main clinical groups of PH,

*i.e.* pulmonary veno-occlusive disease (PVOD; group 1′), PH due to lung diseases (group 3), chronic thromboembolic pulmonary hypertension (CTEPH; group 4), and some heterogeneous and rare conditions included in group 5, are less frequent indications of LTx in pulmonary vascular disease [1]. PH due to left heart disease (group 2) is classically not an indication for isolated LTx. This article mainly covers the issue of LTx in PAH.

The number of patients receiving transplants for PAH have progressively fallen worldwide. PH accounts for just 2–3% of all indications during recent years compared with 11–13% 20 years ago [1]. The advent of effective targeted medical therapy for PAH and the continued worldwide problem of donor lung shortage have led to a significant reduction in the number of patients with PAH undergoing transplantation. Nevertheless, the long-term outcomes of medically treated patients remain uncertain and LTx will remain an important mode of therapy for those who fail on such therapies. Studies indicate that up to 25% of patients with IPAH may fail to improve on disease-targeted therapy and the prognosis of patients who remain in World Health Organization (WHO) functional class III–IV remains poor.

## Choice of transplant operation

Historically, there have been three operative procedures used in patients with PAH, with each procedure having its own advantages, including single-lung transplantation (SLTx) [3–7], sequential bilateral lung transplantation (SSLTx) [8] and heart/lung transplantation (HLTx) [9–11].

The haemodynamic consequences of PH with right ventricular (RV) hypertrophy and relative left ventricular (LV) underfilling will lead to changes in the early post-operative period after LTx. This haemodynamic adaptation dramatically increases the risk of pulmonary oedema and primary graft dysfunction (PGD) compared with other indications. The risk of PGD is highest in patients with PAH treated by SLTx compared with SSLTx or HLTx.

Early proponents of SLTx argued that it is technically an easier procedure to perform, has less morbidity and mortality than SSLTx or HLTx, and enables more patients to receive lung transplants. Opponents argued that patients transplanted with a single lung are more at risk not only from developing severe post-operative pulmonary oedema [4, 12], but also from incurring severe ventilation/perfusion mismatches in the case of acute or chronic lung allograft dysfunction, and a reduced functional reserve [13, 14], both adversely affecting early and late survival, and functional outcome. Any dysfunction that changes compliance in the allograft can lead to rapid and sometimes marked hypoxaemia in the recipient due to further shifting of ventilation from the allograft to the native lung. Early graft dysfunction due to reperfusion injury may be extremely difficult to manage, leading to severe hypoxaemia and haemodynamic instability. PGD may result and is often associated with prolonged ventilation and risk of infection [4]. SLTx is a satisfactory procedure in patients with PH secondary to pulmonary parenchymal diseases (group 2), with no differences in outcome when compared to patients without PAH [15].

Proponents of SSLTx have argued that this procedure results in fewer ventilation/perfusion mismatches and, as a result, patients are easier to look after in the immediate post-operative period. Moreover, this allows more marginal donor lungs to be used and, hence, makes the best of the rare resource of donor lungs. Patients also have improved pulmonary function and increased long-term survival.

Historically, HLTx was the first and only procedure in PAH patients [16]. Advocates of this procedure argue that this operation is technically more straightforward than SLTx and, thus, associated with fewer post-operative complications [11]. Opponents of this procedure argue that isolated LTx will result in immediate and long-term normalisation of pulmonary vascular resistance (PVR) and RV ejection fraction [5, 6, 17, 18]. The donor heart can be used for isolated cardiac transplantation (so-called domino transplantation). Patients subjected to HLTx are also at risk of accelerated graft coronary disease (transplant vasculopathy), although the incidence in the series from Stanford University (Stanford, CA, USA) was only 8% at 5 years following the

transplant [11]. For all these reasons, many authors have pointed out that HLTx should be reserved for special indications, such as patients with Eisenmenger's syndrome caused by congenital heart disease, and the results are better in patients with a ventricular septal defect (VSD) [11, 19].

No prospective randomised studies have been conducted to relieve the uncertainty as to the best lung transplant procedure for patients with PH. In practice, the vast majority of patients (more than 90%) now receive SSLTx, with a smaller group receiving HLTx.

Four single-centre studies have reported the outcomes between different transplant types for both primary and secondary hypertension. CHAPELIER *et al.* [20] reported on the results of HLTx, SSLTx and SLTx for PAH. There was a similar improvement in early and late right-sided haemodynamic function, pulmonary function, and 2- and 4-year survival rates between HLTx and SSLTx recipients. The sole patient who received a single lung developed severe pulmonary oedema, LV failure, persistent desaturation and an important ventilation/perfusion mismatch. They concluded that HLTx and SSLTx were equally effective but SLTx should be avoided. The Pittsburgh group reported on their experience, which was published in 1994 by BANDO *et al.* [21], that mean pulmonary artery pressure ($P_{pa}$) decreased in all three allograft groups; however, $P_{pa}$ in the SLTx recipients remained significantly higher when compared with the other two groups. A significant ventilation/perfusion mismatch occurred in the SLTx recipients, but not in the others, because of preferential blood flow to the allograft. Graft-related mortality was significantly higher and overall functional recovery was significantly lower at 1 year in the SLTx recipients compared with SSLTx and HLTx recipients. The authors concluded that SSLTx is a more satisfactory option for patients with PH and that HLTx should be preserved for recipients with complex congenital heart diseases or LV dysfunction. Finally, the group at Johns Hopkins Hospital (Baltimore, MD, USA) have reported their results in 57 recipients with primary and secondary PH [22]. The survival up to 4 years in patients with primary PH was superior in SSLTx compared with SLTx recipients (100% *versus* 67%, p=0.02). There was no clear advantage to SLTx *versus* SSLTx for secondary PH, although 4-year survival was better in SLTx recipients if $P_{pa}$ was no more than 40 mmHg (91% *versus* 75%, p=0.11) and it was better in SSLTx if this value was at least 40 mmHg (88% *versus* 62%, p=0.19). The authors concluded that SSLTx is the procedure of choice for patients with PAH and those with secondary hypertension with $P_{pa}$ of at least 40 mmHg. Data from Japan on living lobar transplantation for PAH has shown excellent results [23]. In the future, *ex vivo* lung perfusion with a subsequent lower risk of PGD may offer improved outcome for SLTx in PAH [24].

Recent data from the registry of the International Society for Heart and Lung Transplantation (ISHLT) demonstrate that, since 2008, virtually all isolated-lung transplantations for PAH worldwide are now carried out using SSLTx [1] and that SLTx is no longer considered to be a suitable approach.

## Criteria for candidate selection and timing of transplantation

The goal of LTx is to improve survival and quality of life. Usually, to prolong survival by LTx, natural expected survival without LTx should be lower than 50%. LTx is a high-risk surgical procedure with a 3-month mortality of approximately 10–20%, depending on the condition of the patient. General contraindications for candidate selection should be respected facing the situation of donor shortage. The ISHLT recommends an upper age limit for transplantation of 65 years, although there are variations between centres and countries reflecting local views. The age criterion is influenced by data showing a progressive increase in mortality for procedures in patients over the age of 55 years [1]. Patients who develop end-stage pulmonary vascular disease failing on medical therapy may be considered for LTx provided that they conform to other criteria below.

The presence of uncontrolled systemic disease in addition in respiratory failure precludes LTx. Good renal function is essential in view of calcineurin-inhibitor toxicity and a creatinine clearance of more than 50 $mL \cdot min^{-1}$ is required. In severe PH, developing kidney failure usually indicates

pre-renal kidney failure due to low cardiac output. Nevertheless, independent kidney disease should be ruled out in this situation. Only minor abnormalities of liver function are acceptable, with no abnormalities of coagulation. A raised hepatic alkaline phosphatase level with minimal elevation of transaminases requires investigation, but does not preclude assessment. PH is occasionally seen in patients with cirrhosis [25] and, hence, it is important to exclude the presence of this in patients with PH and abnormal liver function tests. Severe hepatic congestion may occur in patients with terminal PH. Elevated bilirubin, especially an increase in bilirubin of 50%, usually indicates progressive disease, and does not preclude LTx by itself.

The timing of referral for patients with PH remains a difficult area, though there is true consensus in two specific diagnoses. Patients with PVOD (group 1′) and pulmonary capillary haemangiomatosis (PCH) who do not respond to medical therapy in the main that should be referred for LTx consideration at diagnosis, providing that they appear suitable regarding general criteria [26, 27].

However, there has been considerable change in the approach to assessing and listing of patients with severe PAH since the development of targeted medical therapy. Until the 1990s, medical treatment had focused on non-disease-specific therapy based on calcium channel blockers (CCBs), anticoagulants, diuretics, digoxin and oxygen. In the US National Institutes of Health (NIH) registry of 1991 [28], the median survival was 2.8 years and, hence, patients were generally referred for transplantation consideration when they had reached functional class III–IV. The development of new drugs, and combination medical therapies with prostaglandins (PGs), endothelin receptor antagonists (ERAs) and phosphodiesterase inhibitors has clearly impacted greatly on the timing of transplant listing. Moreover, two studies have demonstrated that 60–70% of patients who had previously been listed for transplantation on pre-epoprostenol criteria can be de-listed because of clinical improvement [22, 29]. The most recent survival data for the ISHLT registry suggest a 5-year survival in recipients with PAH of approximately 50% following HLTx or SSLTx [1]. However, PAH is one of the major risk factors for both early and late mortality, with an odds ratio of 1.52 due to the increased risk of post-operative PGD [1].

It is in this setting that PH and transplant centres must decide whom to refer for listing and the timing of such a referral. One study, by PIELSTICKER *et al.* [30], surveyed current practices in a wide variety of transplant centres throughout North America, Europe and Australia. 40% of centres felt all functional class III patients should be referred to transplant centres. By contrast, 57% of centres limited referral to those functional class III–IV patients who had failed to show benefit after an average of 3 months of epoprostenol therapy. A recent single-centre report has demonstrated the value of assessment after 3 months of epoprostenol therapy. An improvement in function to functional class II and a decrease in PVR of 30% or more is associated with a survival of 90% at 5 years.

Only 40% of centres use one or more haemodynamic criteria for listing. These include a mean right atrial pressure ($P_{ra}$) of more than 15 mmHg, PVR of 4–15 Wood units, a mixed venous oxygen saturation of less than 63% and a cardiac index of less than 2 $L \cdot min^{-1}$ [31, 32]. The vast majority of centres use some form of exercise testing and echocardiography to help determine functional status referral and listing [33]. No single measurement on echocardiogram has emerged as the most useful. The evidence suggests, however, that exercise testing can be more helpful. A 6-minute walking distance (6MWD) of more than 300 m is associated with a good prognosis, and this simple exercise test is both reproducible and correlates reasonably well with haemodynamics. It is also very sensitive in the detection of improvements related to therapy. Cardiopulmonary exercise testing with metabolic gas exchange is used by a minority of centres where a mean oxygen consumption of less than 10 $mL \cdot kg \cdot min^{-1}$ is used as an indicator for listing a patients for LTx.

Overall, the results show that major PH and transplant centres vary considerably regarding patterns of referral, listing and transplantation of patients, and it is only with continued, carefully collected registry data that guidelines for best practice will be refined. One important issue relates to the potential delay for a functional class IV patient who fails to respond to intravenous prostanoid over 3 months in being listed for a transplantation and the effect this has on their overall chances of receiving a graft. Patients who remain in a stable clinical state at functional class

III will also prove a potentially difficult group and it is suggested that careful note is taken of the patients' informed views in this situation.

Patients who are experiencing problems with exertional syncope but who otherwise seem to have a good quality of life should be considered for atrial septostomy in addition to receiving prostanoid therapy.

Finally, potentially life-threatening haemoptysis should also be considered an indication for placing a patient on the LTx list. A suggested guideline for transplant listing is shown in table 1.

International guidelines suggest a functional class III–IV and rapidly progressive disease as criteria for referral of candidates with PAH. The same group of experts suggest admitting PAH patients on the waiting list when functional class III–IV persists on maximal medical therapy, the 6MWD falls below 350 m, they fail to improve with *i.v.* epoprostenol, or equivalent, and they have a cardiac index of less than 2 $L \cdot min^{-1} \cdot m^{-2}$ or $P_{ra}$ exceeding 15 mmHg [34].

Data from 2,716 patients with PAH who had been consecutively enrolled in the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), were analysed to assess predictors of 1-year survival. Key predictors of survival based on the patient's most recent evaluation were derived from a multivariable, weighted risk formula for clinical use. 1-year survival from the date of enrolment was 91.0%. Variables independently associated with increased mortality included PVR above 32 Wood units, PAH associated with portal hypertension, modified functional class IV, being male and aged over 60 years, and a family history of PAH. Renal insufficiency, PAH associated with connective tissue disease (CTD), functional class III, mean $P_{ra}$, resting systolic blood pressure and heart rate, 6MWD, brain natriuretic peptide (BNP), diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) % predicted, and pericardial effusion on echocardiogram all predicted mortality (fig. 1) [35]. Another problem is that the registries do not represent incident case series.

In 2005, lung allocation for transplantation in the USA changed from a system based on waiting time to a system based on the Lung Allocation Score (LAS) for patients aged 12 years and older [36]. The LAS is a numerical value used to assign relative priority for distributing donated lungs for transplantation. The LAS takes into account various measures of a patient's health in order to direct donated organs towards the patients who would best benefit from a lung transplant [36]. In contrast to the other diagnosis groups, systolic and mean $P_{pa}$ proved not to predict waiting list survival in PAH patients.

**Table 1.** Indications and contraindications for transplant in pulmonary hypertension

| |
|---|
| **Indications** |
| FC III–IV despite trial of combination therapy, including PG therapy, for 3 months |
| Useful haemodynamic parameters |
| Cardiac index <2 $L \cdot min^{-1} \cdot m^{-2}$ |
| Mean $P_{ra}$ > 15 mmHg |
| 6MWD <300 m |
| Clinical findings |
| Major haemoptysis |
| Pericardial effusion |
| Progressive right heart failure (worsening kidney function, hyperbilirubinaemia, rising BNP, recurrent ascites) |
| **Major contraindications** |
| Age >65 years |
| Current use of corticosteroids >20 $mg \cdot day^{-1}$ |
| Nutritional issues: BMI <17 or >30 $kg \cdot m^{-2}$ |
| Tobacco and/or substance abuse without prolonged abstinence |
| Untreated/unresolved psychosocial problems |
| Systemic diseases with multiple end-organ damage |
| Active malignancy within 2 years |
| Hepatitis B and C with biopsy-proven cirrhotic liver disease |

FC: functional class; PG: prostaglandin; $P_{ra}$: right atrial pressure; 6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; BMI: body mass index.

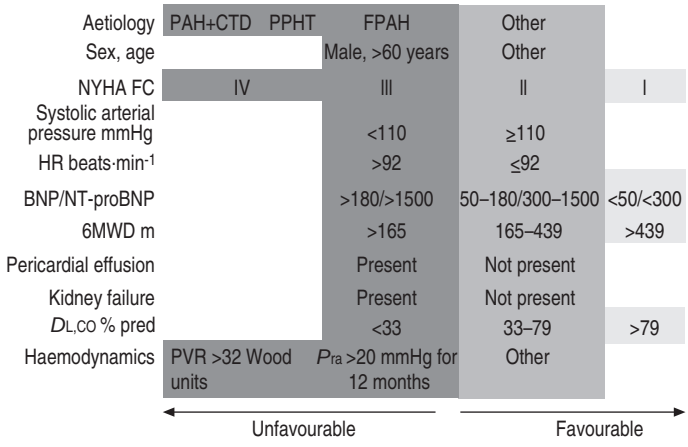


**Figure 1.** Multivariate model derived from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) to predict 1-year survival (n=2,716; 78% females; median age 50 years; 46% pulmonary arterial hypertension (PAH) patients). CTD: connective tissue disease; PPHT: portopulmonary hypertension; FPAH: familial pulmonary arterial hypertension; NYHA: New York Heart Association; FC: functional class; HR: heart rate; BNP: brain natriuretic peptide; NT: N-terminal; 6MWD: 6-minute walking distance; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; PVR: pulmonary vascular resistance; $P_{ra}$: right atrial pressure.

The LAS system is still being evaluated and revised. The reason for this continuing analysis is the need to balance, on one hand, the desire to help those patients in direst need and, on the other, the statistical likelihood of the patient surviving the procedure, as well as the post-operative risks of infection and transplant rejection [36]. In a recent analysis, 7,952 adults from the US transplant registry with a diagnosis of PAH, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) or CF were included to study the effect of the LAS on LTx for IPAH compared with other major diagnoses. Waiting list mortality decreased for every diagnosis except PAH, which remained unchanged. Implementation of the LAS was not associated with changes in post-transplant mortality for any diagnosis. Under the LAS system, patients with PAH were less likely to be transplanted than patients with IPF or CF and at greater risk of death on the waiting list than patients with COPD or CF, after adjustment for demographics and transplant type. Post-transplant mortality for IPAH was not statistically different from that of other diagnoses [37]. 2,327 patients with PAH enrolled in the REVEAL registry and had all required variables available to compute the LAS and were included in a recent analysis [38]. Uni- and multivariable analyses were conducted to compare waiting list survival predicted by the LAS formula with that observed in the REVEAL cohort. The authors identified two variables independently associated with increased mortality compared with that predicted by the LAS in multivariable analysis using a Cox proportional hazards model. The first was mean $P_{ra}$ more than or equal to 14 mmHg and, secondly, a 6MWD less than or equal to 300 m. These results from analysis of the REVEAL registry cannot be transferred exactly to the transplant situation, because transplant candidates may differ in terms of age and comorbidities, and the REVEAL registry does not cover post-transplant survival. Based on registry analysis, in the USA, a change (increase) in bilirubin of at least 50%, occurring in a 6-month period, was added to the LAS for patients with PH. Figure 2 summarises a proposed treatment flow-chart taking into account recent registry data.

## Bridging to transplantation

Patients who are failing on medical therapy may develop severe right heart failure while actively listed for transplantation. Consideration should be given to atrial septostomy in such patients, providing they conform to the guidelines for this procedure. The use of an oxygenating membrane device in a bypass circuit from pulmonary artery to left atrium, the so-called oxygenating septostomy, has also been successfully employed. Successful bridging with use of extracorporeal membrane oxygenation (ECMO) in awake PH patients has been described [39]. A pulmonary artery-to-left atrium approach was described recently as a bridge to thoracic organ transplantation in four patients with PAH using a pumpless lung-assist device [40]. In contrast to inguinal cannulation of ECMO, this technique required sternotomy and general anaesthesia.

## Complications

PGD is a severe, acute lung injury occurring early after LTx that is responsible for significant morbidity and mortality [41]. Previous studies have demonstrated that primary PAH is known to be a risk factor for PGD. PGD occurs in 10–30% of recipients, and is characterised by hypoxaemia, increased capillary permeability, ventilation/perfusion mismatch and radiographic infiltrates, all occurring within the first 72 post-operative hours [42]. The haemodynamic consequences of PH with RV hypertrophy and LV underfilling predispose to PGD during the early post-operative period after LTx, and are greatest in SLTx and suprasystemic $P_{pa}$. In LTx, ECMO is currently accepted to treat post-operatively arising severe primary graft failure [43]. There is recent interest in the potential of prolonged ECMO support in the post-operative period to reduce the risk of PGD in PH patients.

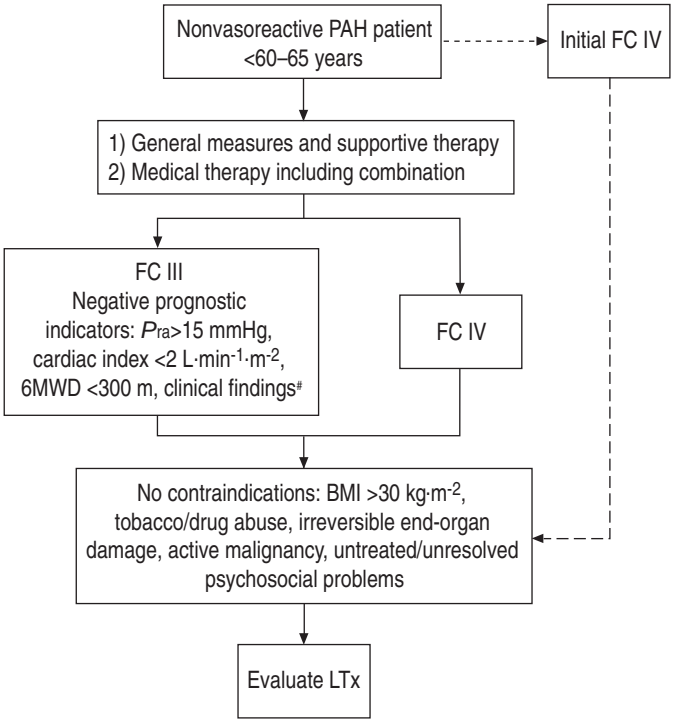


**Figure 2.** Treatment algorithm for potential lung transplantation (LTx) candidates with pulmonary arterial hypertension (PAH). FC: functional class; $P_{ra}$: right atrial pressure; 6MWD: 6-minute walking distance; BMI: body mass index. #: pericardial effusion, kidney failure, hyperbilirubinaemia or major haemoptysis.

Long-term survival after LTx is mainly impaired by the increases risk of infection and chronic lung allograft dysfunction (CLAD). Obliterative bronchiolitis is the pathological feature of CLAD, which is the major limitation to long-term survival following LTx, affecting approximately SO percent of patients by 5 years. It is defined physiologically by the presence of progressive airflow obstruction clinically termed bronchiolitis obliterans syndrome (BOS). It is associated with both an increased frequency and persistence of acute vascular rejection, but there are numerous nonallogenic associations now described, including viral and bacterial infections, and gastro-oesophageal reflux. Although PGD is a potential risk factor for CLAD, there is no evidence of increased incidence of CLAD in transplanted patients with PH.

## Results

Unadjusted 3-month mortality rates after transplantation is highest in IPAH (24%), sarcoidosis (17%) and IPF (15%), and lowest in COPD (9%), most probably due to differences in early complications, such as PGD [1]. In contrast to the overall survival rates, 5-year survival among patients surviving for at least 1 year was significantly improved in recipients with IPAH (72%) than in those with COPD (62%) and IPF (61%). The ISHLT registry shows a 1-year survival of 70% with a 5-year survival of approximately 50% following LTx for PAH. Functional results in survivors measured in terms of both forced expiratory volume in 1 second ($FEV_1$) and exercise performance are good, with patients returning to New York Heart Association (NYHA) functional class I from their pre-operative level of functional class III–IV. Recipients can expect to attain their normal predicted $FEV_1$ and vital capacity (VC) by 1 year in the absence of complications if they receive two new lungs, although $D_{L,CO}$ usually remains reduced. All patients should expect restoration of a normal lifestyle with little or no functional restriction during normal activities of

daily living. Exercise data comparing 6MWD and maximum oxygen consumption during an incremental, symptom-limited exercise test show that recipients of successful transplants, irrespective of the operation, return to a normal 6MWD of 600 m or greater by 1 year with no evidence of desaturation on exercise. The maximum oxygen consumption is significantly greater in HLTx and SSLTx compared with SLTx alone. However, maximum oxygen consumption during a symptom-limited test remains at around 50% pred for a given subject in the first year, in part due to decompensation on account of the pre-transplant disability. Nevertheless, the functional results allow restoration of a comfortable lifestyle.

There has been great interest in the study of lungs after successful LTx to see if the acquired lung disease will recur in the allografts. To date, there is no evidence of idiopathic PH returning in lung grafts. Vascular sclerosis of pulmonary vessels is seen in all patients who have obliterative bronchiolitis.

### *Statement of Interest*

None declared.

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# Chapter 21

# Pulmonary arterial hypertension in 2020: a glimpse at the future

*Lewis J. Rubin*[*] *and Andrew J. Peacock*[#]

**SUMMARY: Over the past 20 years remarkable progress has been achieved in our understanding of the pathogenesis of pulmonary arterial hypertension (PAH), and in developing targeted treatment for this life-threatening disease. However, despite these achievements, the outcomes of PAH remain poor and delays in diagnosis and initiation of treatment contribute to the unacceptable outcomes. Through global efforts to study this rare disease, we envisage that the next few years will lead to new modalities to facilitate noninvasive diagnosis and monitor the course of disease, as well as novel treatment strategies based on further unravelling the pathogenic processes responsible for its development and progression.**

**KEYWORDS: Cell replacement therapy, magnetic resonance imaging, novel pathways**

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In less than two decades, remarkable advances have been achieved in the development of disease-targeted therapies for pulmonary arterial hypertension (PAH), and the advances in our understanding of the pathogenesis of this condition is rapidly increasing. Despite these achievements, the response to therapy is often incomplete in many PAH patients and survival remains poor. Accordingly, new strategies must be developed for both early diagnosis and treatment of PAH that not only optimise the treatments currently available, but also capitalise on the identification of novel pathogenic pathways for PAH. Additionally, since symptoms and signs of PAH often predate the diagnosis by months or even years, the implementation of novel diagnostic techniques, coupled with education at all levels of medical training and experience, are critical for earlier diagnosis and initiation of therapy, which clearly improves outcome. This article will provide a glimpse into the future from our vantage point, as we have witnessed first-hand the achievements over the course of our careers, based on recent developments in the field that hold promise for enhancing the management of PAH.

## Advances in understanding the pathogenesis that may lead to novel therapeutic targets

The identification of mutations in the bone morphogenetic protein receptor type II (BMPR II) in the majority of cases of heritable PAH has been a major advancement in the elucidation of the

pathogenic sequence [1–3]. However, fewer than 20% of individuals with a BMPR II mutation develop heritable PAH, and most individuals with PAH do not have an identifiable mutation [4, 5]. Accordingly, it is likely that other factors, including genetic and environmental stimuli (a second hit), are needed to initiate the pathological sequence that leads to vascular injury and the pulmonary hypertensive state. The role of these other factors in initiating the vascular injury and the mechanisms through which they interface with genetic abnormalities are unknown [5]. Additionally, it is unclear whether inherited or acquired abnormalities in BMPR signalling are a common feature of all forms of PAH. Various other cellular pathway abnormalities have been described that may play important roles in the development and progression of PAH [6–21]. These include altered synthesis of nitric oxide, prostacyclin ($PGI_2$) and endothelin, impaired potassium channel and growth factor receptor function, altered serotonin transporter regulation, increased oxidant stress, and enhanced matrix production. However, the relative importance of each of these processes is unknown, and the interactions between these various pathways need to be explored. Additionally, the intermediate steps involved in the transduction of signals related to BMPR II are unknown; clarification of these pathways will lead to a more complete understanding of how impaired BMPR II signalling, both inherited and acquired, leads to hypertensive pulmonary vascular disease. Novel therapies based on an enhanced understanding of these intermediate steps and interactions could lead to novel therapies that target these pathways, and would be particularly welcome if they were to have broad efficacy across the disease spectrum (fig. 1).

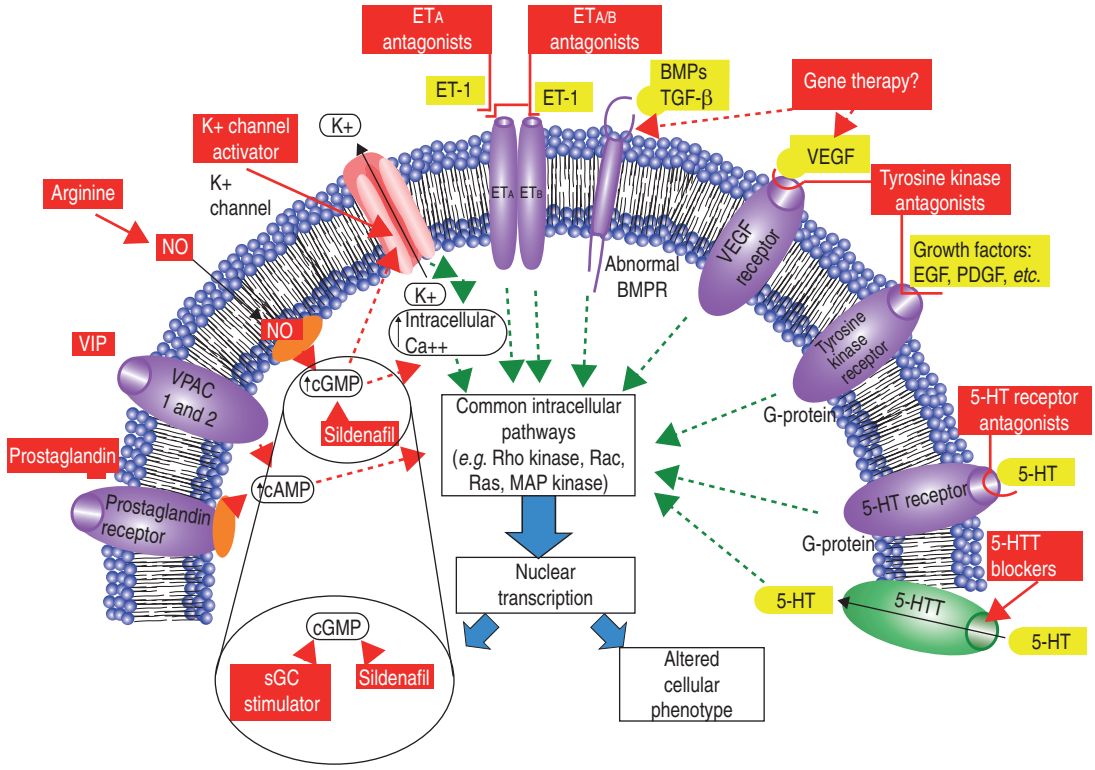


**Figure 1.** Schematic diagram of a pulmonary vascular cell showing the possible mechanisms leading to vasoconstriction and/or proliferation of the pulmonary vascular component cells. The current or possible future treatments that could be used to reverse these processes are also shown. VIP: vasoactive intestinal peptide; VPAC: VIP receptors; NO: nitric oxidase; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; ET-1: endothelin-1; ETA: endothelin A; ETB: endothelin B; BMP: bone morphogenetic protein; TGF-β: transforming growth factor-β; MAP: mitogen-activated kinase; BMPR: bone morphogenetic protein receptor; VEGF; vascular endothelial growth factor; EGF: endothelial growth factor; PDGF: platelet-derived growth factor; 5-HT: 5-hydroxytryptamine; 5-HTT: 5-hydroxytryptamine transporter.

# Optimising therapy for PAH

## Maximising efficacy of current therapies

Approximately a decade ago, the treatment of PAH was based on a limited understanding of the disease pathogenesis and was largely empiric and usually ineffective. The treatment of PAH has advanced dramatically since then, with a number well-designed clinical trials demonstrating efficacy of several therapies that target specific abnormalities present in PAH [22–27]. Furthermore, the complexity of these treatments has devolved from continuous intravenous delivery to oral and inhaled modes of drug delivery. However, critical questions regarding the optimisation of our current therapeutic armamentarium remain unanswered. 1) How should therapy be initiated, as monotherapy or in combination? 2) If in combination, which class of agents should be implemented? 3) If monotherapy, which class of agent is best? 4) What criteria should be used to make decisions regarding adding or changing therapies?

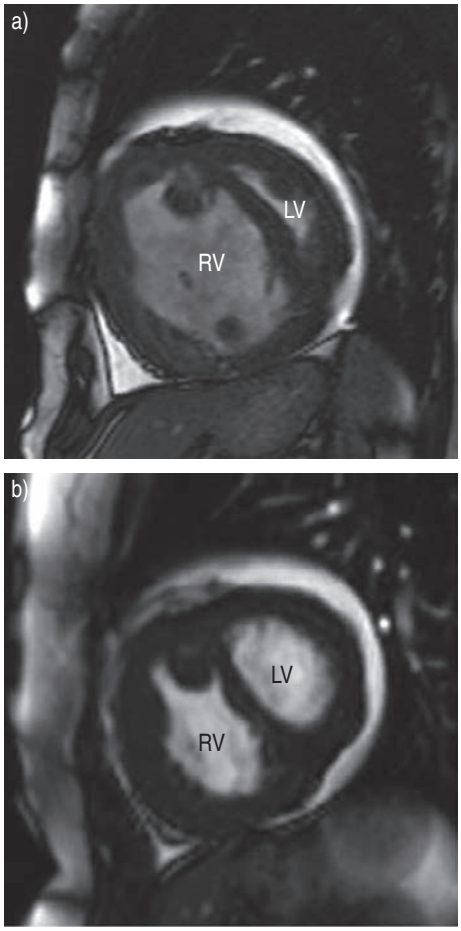


**Figure 2.** Cardiac magnetic resonance image of the right ventricle (RV) and left ventricle (LV) a) before and b) after treatment for pulmonary arterial hypertension. Before treatment there is hypertrophy and dilation of the RV with paradoxical movement of the interventricular septum into the LV and diminished LV end-diastolic volume. After treatment there is still dilation and hypertrophy of the RV but its function is greatly improved because the filling of the LV is now normalised.

Much can be learned from our colleagues who have advanced the treatment paradigms for left heart failure, HIV infection and cancer chemotherapy by addressing similar questions through well-designed, multicentre, global clinical trials. It is probable that, as with the progress in these life-threatening diseases, we will learn over the next few years not only how to best demonstrate long-term efficacy with our treatment strategies for PAH, but will define the optimal strategy for achieving this with currently available targeted therapies.

## Individualised therapy

Several recent publications have demonstrated that infusions of endothelial progenitor cells (EPC) in animal models of pulmonary hypertension (PH) attenuate the injury, particularly when these cells are transfected with nitric oxide synthase, the enzyme responsible for the generation of nitric oxide from the L-arginine precursor [28]. Thus, while cell-based therapies have yet to fulfil their promise in clinical studies, particularly in cardiovascular diseases, pilot safety and efficacy trials are now underway with progenitor cell infusions in patients with severe PAH refractory to medical therapy [29]. Similarly, a milestone was achieved in genomic medicine earlier this year with the approval of Kalydeco (Vertex Pharmaceuticals Inc., Cambridge, MA, USA) for cystic fibrosis (CF), specifically for the subset of patients with the G551D mutation of the CF transmembrane conductance regulator (CFTR) gene. As our understanding of the genetics of PAH evolves, including identification of specific receptor subtypes, a similar approach may be feasible for PAH.

### Treating the right ventricle

All the treatments developed to date have been directed at vasodilation and/or inhibiting the remodelling of the pulmonary circulation. We have taken the view that hypertrophy and the subsequent failure of the right ventricle (RV) are simply a function of the obstructed circulation and improvements in RV function can only be expected if we can improve RV impedance. This remains broadly true, but it has become clear that in some patients (*e.g.* congenital heart disease (CHD)-PH) the heart compensates and functions well whereas in others (*e.g.* systemic sclerosis-PH) the heart fails to compensates and functions poorly. These observations have renewed interest in treating the RV directly and we may see treatments in the future with this aim [30, 31].

## Enhancing early diagnosis and monitoring the course of therapy

The development of treatments for PAH has prompted a radical change in the way physicians view this condition, from an attitude of therapeutic nihilism to one of interest and enthusiasm for treatment. However, early diagnosis remains the key to optimal outcome, and progress in this regard has been hampered by a lack of consideration of PAH as a cause of plebeian symptoms and the necessity of performing invasive procedures to diagnose and optimally monitor the course of treatment. Education of medical practitioners at all levels of training and experience regarding the clinical aspects of PAH, from risk factors and diagnosis to management, should become a high priority. Furthermore, as management becomes more complex, it should be centralised at experienced facilities. Just as certification in niche areas of other subspecialties recognises those who have additional training and knowledge, such as electrophysiology or interventional techniques in cardiology, we envision the development of formalised training and sub-certification in pulmonary vascular medicine. Management of PAH patients at such centres will lead to better and less costly medical care; both of which are factors of increasing importance in the future.

The development of novel biomarkers that specifically relate to the manifestation, severity and response to treatment of PAH and that could be widely available and inexpensively performed will enhance early diagnosis and optimise evolving treatment strategies. Imaging techniques, particularly those that address the state of RV function in PAH, will offer alternatives to invasive studies such as catheterisation. Additionally, techniques such as magnetic resonance imaging (MRI) may be particularly useful since these techniques enable detailed and repeated structural and functional studies of the RV to be performed, which are arguably the most important determinants of outcome (fig. 2) [31].

## Conclusions

Although major advances in our understanding of the mechanism of disease development and in the treatment of PAH have been achieved over the past decades, substantial gaps in our knowledge remain. Bringing together physicians and scientists representing multiple disciplines and expertise, all sharing an overlapping interest in PAH, affords us the opportunity to narrow these knowledge gaps in the future. We believe, therefore, that the management of PAH will improve even further over the next 8 years, and that the future will be even brighter for our patients than it is now.

### *Statement of Interest*

L.J. Rubin has served as an expert witness in legal cases involving PAH. He has also served on the scientific advisory committee for United Therapeutics and as a consultant for NHLBI, Actelion, Pfizer, United Therapeutics, LungLLC, Gilead, Aires, GSK and Bayer. A.J. Peacock has received honoraria and travel grants from Actelion, Pfizer, GSK and United Therapeutics.

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### Educational questions

**1. Which one of the following statements is true? Pulmonary arterial hypertension is defined as:**
❑ A mean pulmonary artery pressure of more than 25 mmHg. ❑ A mean pulmonary artery pressure of more than 25 mmHg and a wedge pressure below 15 mmHg. ❑ A mean pulmonary artery pressure of more than 25 mmHg and a wedge pressure below 15 mmHg, and the exclusion of chronic thromboembolism. ❑ None of these.

**2. Which one of the following statements is true? A high probability ventilation/perfusion scintigraphy in a patient with pulmonary hypertension:**
❑ Is proof of chronic thromboembolic pulmonary hypertension. ❑ Is proof of acute pulmonary embolism. ❑ Requires further investigation before a conclusion can be drawn. ❑ Rules out pulmonary arterial hypertension.

**3. Which one of the following statements is true? Wedge pressure is correctly measured if:**
❑ It is derived from the last complete pressure wave at the end of expiration. ❑ It is the average pressure measured when the balloon is inflated. ❑ The patient received high doses of diuretics prior to the measurement. ❑ It is derived from the average pressure measured during inspiration.

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**4. High cardiac output in a patient with pulmonary hypertension is an unusual finding in which one of the following conditions:**

❑ Sickle cell anaemia. ❑ Idiopathic pulmonary arterial hypertension. ❑ Pulmonary hypertension related to a portocaval shunt. ❑ Pulmonary hypertension related to left to right shunt.

**5. A diagnosis of portopulmonary hypertension may be more likely in which of the following clinical situations? Select all that are correct**.

❑ A history of previous portocaval shunt surgery. ❑ A diagnosis of autoimmune hepatic disorders. ❑ Cirrhosis with echocardiography suggesting a right ventricular systolic pressure of >50 mmHg. ❑ Cirrhosis with electrocardiogram showing a left bundle branch block. ❑ During evaluation for liver transplantation.

**6. Which one of the following statements is true? Screening for portopulmonary hypertension in liver transplant candidates is *best* accomplished by the use of:**

❑ Chest radiography. ❑ Dobutamine stress echocardiogram. ❑ Transthoracic echocardiogram. ❑ Transoesophageal echocardiogram. ❑ Electrocardiogram.

**7. Right heart catheterisation confirms the diagnosis of portopulmonary hypertension. Which one of the following results would *not* be consistent with that diagnosis?**

❑ Mean pulmonary artery pressure 35 mmHg. ❑ Cardiac output 8.5 $L \cdot min^{-1}$. ❑ Pulmonary capillary wedge pressure 12 mmHg. ❑ Pulmonary vascular resistance 220 $dyn \cdot s \cdot cm^{-5}$.

**8. Which one of the following statements is true? The highest risk during a liver transplant operation in the setting of portopulmonary hypertension is during:**

❑ Intubation. ❑ Anaesthesia induction. ❑ Anhepatic phase. ❑ Reperfusion.

**9. Which one of the following statements is true? Portopulmonary hypertension:**

❑ Is an absolute contraindication to liver transplant. ❑ Is diagnosed only in adults with liver cirrhosis. ❑ Frequently precedes the diagnosis of hepatopulmonary syndrome. ❑ Is not related to the severity of portal hypertension.

**10. Which one of the following statements is true? If the mean pulmonary artery pressure is documented to be 65 mmHg at the time of liver transplant operation:**

❑ The transplant procedure should be cancelled. ❑ IV digoxin should be started and the case continued. ❑ IV metoprolol should be started and the case continued. ❑ IV nitroprusside should be started and the case continued.

**11. Which one of the following statements concerning chronic thromboembolic pulmonary hypertension is true?**

❑ The condition mainly affects young females. ❑ On average, chronic thromboembolic pulmonary hypertension patients are younger than pulmonary arterial hypertension patients. ❑ The mean age at diagnosis is over 60 years. ❑ A vast majority of patients are male smokers. ❑ Thrombus load is age-dependent.

**12. Which one of the following statements is true?**

❑ Pulmonary thromboembolism is a classic risk factor for chronic thromboembolic pulmonary hypertension. ❑ Chronic thromboembolic pulmonary hypertension can be treated by thrombolytic therapy. ❑ Oral anticoagulation is indicated in cases with a history of symptomatic venous thromboembolism. ❑ Chronic thromboembolic pulmonary hypertension patients are predominantly female. ❑ Bronchial collaterals are uncommon in chronic thromboembolic pulmonary hypertension.

**13. Which one of the following statements is true? The method of choice to screen for chronic thromboembolic pulmonary hypertension is:**
❑ Perfusion magnetic resonance imaging. ❑ Perfusion scintigraphy. ❑ Computed tomography angiography. ❑ Contrast echocardiography. ❑ Optical coherence tomography.

**14. Which one of the following statements is true? Chronic thromboembolic pulmonary hypertension can be diagnosed if one or more mismatched segmental or larger perfusion defect is detected:**
❑ In combination with dyspnoea. ❑ In the presence of a family history of recurrent venous thromboembolism. ❑ In the presence of a central venous catheter. ❑ In combination with precapillary pulmonary hypertension. ❑ And plasma factor VIII is elevated.

**15. Which one of the following statements is not true?**
❑ A pulmonary hypertensive crisis describes a hyper-acute rise of systolic pulmonary pressure (>50% of systemic pressure) due to any cause. ❑ Acute right ventricular failure in the setting of increased afterload may be termed acute cor pulmonale. ❑ Acute cor pulmonale can occur due to the effects of positive pressure ventilation. ❑ One-lung ventilation as required for a video-assisted thoracoscopic procedure is unlikely to have adverse haemodynamic effects. ❑ The insufflation of carbon dioxide required for laparoscopic surgery may impair right ventricular function both by causing acute hypercapnic acidosis resulting in increased pulmonary vascular resistance and heart rate, and through abdominal distension lowering right ventricular preload.

**16. Which one of the following is unlikely to cause adverse effects on the pulmonary circulation?**
❑ Poorly controlled pain. ❑ Laryngoscopy at induction of anaesthesia . ❑ High positive end-expiratory pressure settings during positive pressure ventilation. ❑ Episodes of desaturation during anaesthesia. ❑ Intravenous frusemide.

**17. Which one of the following statements is true? Cardiothoracic procedures at high risk of peri- or post-operative pulmonary hypertension include:**
❑ Pulmonary endarterectomy. ❑ Closure of a patent foramen ovale following embolic stroke (with normal right atrial pressure). ❑ Corrective congenital cardiac surgery for a ventricular septal defect. ❑ Mitral valve replacement surgery. ❑ Pneumonectomy.

**18. Risk factors for perioperative complications in patients with pre-existing pulmonary hypertension undergoing general surgery include which one of the following?**
❑ Short operative time. ❑ Emergency surgery. ❑ Low preoperative pulmonary vascular resistance. ❑ Use of sevoflurane as an inhalational anaesthetic agent. ❑ High pre-operative 6-minute walk distance.

**19. Which one of the following is not a treatment of perioperative pulmonary hypertension:**
❑ Intravenous prostacyclin. ❑ Levosimendan. ❑ Inhaled nitric oxide. ❑ Inhaled iloprost. ❑ Inhaled nitrous oxide.

**20. Management of perioperative acute cor pulmonale may include which one of the following?**
❑ Levosimendan. ❑ Intravenous diltiazem. ❑ Administration of one litre of Hartmann's solution. ❑ Oxytocin. ❑ Aldosterone.

**21. All except one of the following should be discussed in a multi-disciplinary meeting. Please mark which factor should not be discussed.**
❑ Where to perform surgery (local hospital or pulmonary hypertension centre). ❑ When to stop pulmonary vasodilator therapies. ❑ When to stop warfarin. ❑ The emergency plan for pulmonary hypertensive crises should be discussed with the anaesthetic team. ❑ The plan for post-operative haemodynamic monitoring in the intensive care unit or high-dependency unit.

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**22. Which one of the following statements is true? Selexipag is a:**
❑ Growth factor inhibitor. ❑ Guanylate cyclase stimulator. ❑ Prostacyclin I receptor agonist. ❑ Neurotransmitter hormone.

**23. Which one of the following statements is true?**
❑ Inhaled treprostinil has been licensed for use in Europe since 2005. ❑ Inhaled treprostinil has shown beneficial effects on pulmonary haemodynamics in a randomised controlled trial. ❑ Inhaled treprostinil has a similar incidence of systemic effects as inhaled iloprost. ❑ None of these.

**24. Which one of the following statements is true? Riociguat is administered:**
❑ Orally. ❑ By inhalation. ❑ Subcutaneously. ❑ Intravenously.

**25. Which one of the following statements is true? Endothelial progenitor cells are derived from:**
❑ Growing blood vessels. ❑ Embryos. ❑ The lungs. ❑ Bone marrow.

**26. Which one of the following statements is true?**
❑ Riociguat has been investigated in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, showing reduced pulmonary vascular resistance, improved 6-minute walking distance and improved N-terminal pro-brain natriuretic peptide at 12 weeks. ❑ Riociguat has been investigated in patients with pulmonary hypertension due to chronic hypoxia, showing reduced pulmonary vascular resistance, improved 6-minute walking distance and improved N-terminal pro-brain natriuretic peptide levels at 12 weeks. ❑ Riociguat has been investigated in phase III clinical trials of pulmonary arterial hypertension patients, showing improved mean pulmonary artery pressure and cardiac index. ❑ Riociguat has been investigated in a phase II clinical trial of pulmonary arterial hypertension patients, showing worsening pulmonary vascular resistance but improved 6-minute walking distance and cardiac index.

**27. Which one of the following statements is true?**
❑ Rho-kinase inhibitors have yet to demonstrate efficacy in a randomised controlled trial of pulmonary arterial hypertension. ❑ Rho-kinase inhibitors reduce smooth muscle cell proliferation and inflammatory cell migration. ❑ Rho-kinase inhibitors confer improvements in survival in animal models of pulmonary hypertension. ❑ All of these.

**28. Which one of the following statements is true? The operation of choice for patients with idiopathic pulmonary hypertension refractory to medical therapy is:**
❑ Single lung transplantation. ❑ Bilateral lung transplantation. ❑ Heart lung transplantation. ❑ Pulmonary thromboendarterectomy.

**29. Which of the following statements are true? (Select all that apply.) Major contraindications to transplant referral include:**
❑ Body mass index greater than 30 $kg \cdot m^{-2}$. ❑ Creatinine clearance less than 75 $mL \cdot min^{-1}$. ❑ Cardiac output less than 2.0 $L \cdot min^{-1}$. ❑ Continued smoking.

**30. Transplantation for idiopathic pulmonary arterial hypertension is associated with which one of the following?**
❑ A 5-year survival rate of 20%. ❑ Improved quality of life. ❑ Recurrence of idiopathic pulmonary arterial hypertension at around 5 years. ❑ Less chronic allograft dysfunction (bronchiolitis obliterans syndrome) than transplantation for chronic obstructive pulmonary disease.

**31. Which one of the following complications is more frequent in transplantation for idiopathic pulmonary arterial hypertension compared with other indications?**
❑ Primary graft dysfunction. ❑ Pneumonia. ❑ Chronic lung allograft dysfunction. ❑ Acute rejection.

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